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ACADEMY OF MEDICINE TORONTO

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J. A. Capps	J. A. Capps

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W. T. Belfield	W. T. Belfield
C. D. Wescott	C. D. Wescott
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N. S. Davis	D. J. Davis
Robert B. Preble	S. J. Walker
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Frank Cary	J. Gordon Wilson

FELLOWS

Abbott, Don P.
Abt, Isaac Arthur
Adler, Herman M.
Alexander, Wm. G.
Andrews, Edmund
Andrews, Edward Wyllys
Andrews, Frank Taylor

Babcock, Robert Hall
Bacon, Charles Sumner
Baer, Jos. L.
Barnes, Walter S.
Bassoe, Peter
Baum, William L.
Baxter, George Edwin
Becht, Frank C.
Belfield, William Thomas
Bensley, Robert Russell
Bevan, Aurthur Dean
Billings, Frank
Black, Arthur D.
Black, Robert A.
Blatchford, Frank W.
Bloch, Leon
Blue, Robert
Brawley, Frank
Brenneman, Joseph
Bridge, Norman
Brown, Edward Vail Lapham
Brown, Ralph C.
Brown, Sanger
Buford, Coleman Graves
Burmeister, Wm. H.

Capps, Joseph Almarin
Carlson, Anton Julius
Cary, Eugene
Cary, Frank
Cheney, Henry William
Child, Charles Manning
Church, Archibald
Clark, Wendell J.
Coleman, Geo. H.
Colwell, Nathan Porter
Crowder, Thomas R.
Culver, Harry
Curtis, Arthur Hale

Dagg, Thomas L.
Danforth, William Clark
*David, Frank E.
David, Vernon C.
*Davis, Achilles
Davis, Carl Braden
Davis, David John
Davis, Geo. G.
*Davis, Nathan Smith
Davis, Nathan Smith III
Davison, Chas. A.
DeLee, Joseph Bolivar
Dick, George Frederick
Dodd, Oscar
Dodson, John Milton
Doering, Edward James

Eisendrath, Dan'l N.
Elliott, Arthur R.
Elliott, Charles Addison
Ellis, John Bernard
Falls, Frederick H.
*Favill, Henry Baird
Favill, John
Fishbein, Morris
Frank, Ira
Frankenthal, Lester Emanuel
Frick, Anders
*Friedberg, Stanton Abeles
Friedman, Joseph C.
Frothingham, Herbert H.
Futterer, Gustav

Gamble, William Elliot
Gardiner, Edwin J.
Gatewood, Lee C.
Gay, Robert J.
Gentles, Harry Wernieke
Gerstley, Jesse Robert
Gethro, Fred W.
Gill, James Cornelius
Gilmer, Thomas Lewis
*Gilmore, Robert Tracy
Goodkind, Maurice L.
Green, George Willard
Greer, Jas. R.
Grulee, Clifford Groselle

Haines, Walter Stanley
Hall, George Washington
Halstead, Albert Edward
Hamburger, Walter Wile
Hamill, Ralph C.
Hamilton, Alice
Harkins, Wm. Draper
*Harris, Frederick Gillette

*Deceased

FELLOWS—Continued

Harris, Malcolm La Salle
Harsha, William McIntyre
Harvey, Basil Coleman Hyatt
Hatton, Edw. H.
Heaney, Noble Sproat
Hektoen, Ludvig
Henderson, Elmer E.
Herbst, Robert H.
Herrick, Charles Judson
Herrick, James Bryan
Hess, Julius H.
Hessert, William
Hoelscher, Julius H.
Holinger, Jacques
Holmes, Rudolph Wieser
Howell, Katharine M.
*Ingalls, Ephraim Fletcher
Irons, Ernest Edward

Jones, Harold E
Jordan, Edwin Oakes

Kampmeier, Otto F.
Kanavel, Allen Buckner
Kendall, Arthur I.
Kerr, Ellis Kirk
Koch, Fred Conrad
Koessler, Karl Konrad
Kretschmer, Herman Lewis
Kuh, Sidney

Lane, Francis Adonijah
LeCount, Edwin Raymond
Levison, Abraham
Lewis, Dean De Witt
Lewis, Thomas Henry
Lieberthal, David
Lillie, Frank Rattray
Loeb, Ludwig Mannheimer
*Long, John H.
Loring, J. Brown
Lounsberry, Benj. F.
Luckhardt, Albert E.

MacKechnie, Hugh N.
Matthews, Sam'l A.
Mayers, Lawrence H.
Marquis, George Paul
McArthur, Lewis Linn
McArthur, Selim W.
McCoy, Herbert N.
McGuigan, Hugh
McKenna, Hugh C.
Menge, Frederick
Miller, Joseph Leggett
Mix, Charles Louis
Mock, Harry Edgar
Moorehead, Frederick Brown
Moore, Josiah J.

Nadler, Walter H.
Nicoll, Homer King
Norcross, Edward Powers
Norton, John Foote
Noyes, Frederick B.

Ochsner, Albert John
Ormsby, Oliver Samuel
Osgood, Luther J.

Paddock, Charles Evart
Parmelee, Arthur H.
Parkes, William Ross
Patrick, Hugh Talbot
Peterson, Wm. F.
Phemister, Dallas Burton
Pierce, Norval Harvey
Pietrowicz, Stephen Roman
Plummer, Samuel Craig
Pollock, Louis J.
Porter, John Lincoln
Portis, Milton Moses
Post, Wilber E.
Potter, Hollis Elmer
Potts, Herbert Anthony
Preble, Robert Bruce
Pusey, Brown
Pusey, William Allen

Quine, William Edward

Ransom, S. W.
Raulston, Burrell O.
Reed, Charles Bert
Reed, Dudley B.
Rhodes, John Edwin
Richter, Harry Mortimer
Ries, Emil
Rothstein, Thor
Ryerson, Edwin Warner

*Sachs, Theodore B.
Sauer, Lewis W.
Saurenhaus, Ernst
Schmidt, Louis Ernst
Schmidt, Otto L.
Sceleth, Charles E.
Shambaugh, George Elmer
Simmons, George H.
Simonds, James P.
Simpson, Elmer E.
Simpson, Frank Edward
Singer, H. Douglas
Sippy, Bertram Welton
Slaymaker, Samuel Robert
Small, Arthur Atwell
Spalding, Heman
Speed, Kellogg
Stevenson, Alexander Francis
Stieglitz, Julius

*Deceased

FELLOWS—Continued

Stillians, Arthur Wm.
Storey, Chas. A.
Swan, Chas. J.
Strouse, Solomon

Tarnowsky, George de
Theobald, Walter
Tice, Frederick
Tieken, Theodore
Tunnicliff, Ruth

Vaughan, Roger Throop
Volini, Camillo

Walker, Samuel Johnson
Washburn, James Murray
Watkins, Thomas James
Weaver, George Howitt
Webster, George W.
Webster, Ralph Waldo
Welker, Wm. H.
Wells, Edward Franklin
Wells, Harry Gideon
Wescott, Cassius D.
Wilder, William Hamlin
Willard, William G.
Williamson, Charles Spencer
Wilson, John Gordon
Woley, Harry P.
Woodyatt, Rollin Turner
Wright, Frank

HONORARY FELLOWS

Frothingham, J. T.
Lusk, Graham
Smith, Theobald
Vaughan, Victor

NON-RESIDENT FELLOWS

Austin, Richard S.
Davis, Benj. F.
Doane, Philip P. S.
Dewey, Richard
Gaarde, F. W.
Harvey, James Alexander
Hoskins, R. G.
Helmholtz, Henry F.
Johnson, Frank
Mathews, Albert Prescott
Moody, Albert M.
Woodruff, Thomas A.
Webster, J. Clarence

CONSTITUT ON AND BY-LAWS

OF THE

INSTITUTE OF MEDICINE

OF CHICAGO

CONSTITUTION

ARTICLE I.

NAME.

The name of this Association shall be the Institute of Medicine of Chicago.

ARTICLE II.

OBJECTS.

The objects of this Institute shall be to promote the study and to encourage the advancement of medicine and allied sciences.

ARTICLE III.

MEMBERSHIP.

SECTION 1. The membership of this Institute shall consist of Fellows, Associates, Honorary Fellows, Life Fellows, and Benefactors. Only the Fellows and Life Fellows and Benefactors shall be eligible for office or have the right to vote. In the event of dissolution of the Association the assets thereof shall be distributed only among the Fellows, Life Fellows and Benefactors, pro rata according to payments made.

SEC. 2. Fellows shall be physicians who are graduates of at least five years' standing of medical schools, or persons engaged in allied scientific pursuits.

SEC. 3. Associates shall be physicians who have been graduates of at least five years' standing of medical schools, and who do not reside within fifty miles of the center of Chicago, or persons engaged in scientific pursuits allied to medicine who do not live within fifty miles of the center of Chicago. In addition, physicians and other persons engaged in scientific pursuits allied to medicine, living within the above prescribed limits, whose income is derived from teaching, or research, or like pursuits, and who, in the judgment of the Board of Governors, are, because of their limited income, entitled to especial consideration in respect of dues, may be elected Associates.

SEC. 4. Honorary Fellows shall be physicians or scientists of distinction.

SEC. 5. Any Fellow of the Institute may upon the payment of $1,000 become a Life Fellow.

SEC. 6. Benefactors shall be persons who have rendered illustrious service, or notable aid to the Institute. They shall be exempt from the payment of dues, but shall be subject in all other respects to the obligations, and shall possess all of the privileges of Fellows.

ARTICLE IV.

BOARD OF GOVERNORS.

SECTION 1. The corporate powers of the Institute shall be vested in a Board of Trustees, called a Board of Governors, fifteen (15) in number, of whom three (3) shall be elected each year. The term of office of each Governor, except the first Governors elected, shall be five (5) years, or until his successor is elected.

SEC. 2. Of the first Governors elected, three (3) shall serve until the first annual meeting; three (3) until the second annual meeting; three (3) until the third annual meeting; three (3) until the fourth annual meeting and three (3) until the fifth annual meeting.

SEC. 3. Any vacancy occurring in the Board from any cause except the expiration of the term of office shall be filled by the Board of Governors, but only for the period between the time of occurrence of the vacancy and the next annual meeting, at which meeting a Governor shall be nominated and chosen to fill out such unexpired term.

SEC. 4. The Board of Governors shall elect all officers and appoint all standing committees of the Institute in accordance with the provisions of Article V of the Constitution; shall have the management and care of all funds and property of the Institute; shall, after proper nomination, elect all Fellows, Associates, Honorary Fellows, Life Fellows, or Benefactors; shall have the power of discipline provided in Article VII; shall manage all of the affairs and business of the Institute either directly or through such officers or agents as it may see fit to authorize.

ARTICLE V.

OFFICERS.

SECTION 1. The officers of the Institute shall be President, Vice-President, Chairman of Board of Governors, Secretary, Treasurer.

SEC. 2. The President shall be elected by a majority vote of the entire Board of Governors, either from their own number or from the Fellowship body, for a period of one year, and may be re-elected only once.

SEC. 3. The Vice-President shall be elected in the same manner as the President, and may be re-elected only once.

SEC. 4. The Chairman of the Board shall be elected by a majority vote of the Board of Governors from their own number for a period of one year.

SEC. 5. The secretary shall be elected by a majority vote of the Board of Governors, either from their own number or from the Fellowship body, for a period of one year.

In the event of the election of the Secretary from the Fellowship body and not from the Board of Governors, he shall have the voting privileges of a Governor.

SEC. 6. The Treasurer shall be elected by a majority vote of the Board of Governors from their own number for a period of one year.

SEC. 7. In the event of the election of the President from the Fellowship body and not from the Board of Governors, he shall have the right to sit with the Board in all its meetings and shall vote as a Governor. The Vice-President shall have the same right in the absence of the President.

ARTICLE VI.

ELECTION OF MEMBERS.

SECTION 1. Election of Fellows, Associates, Honorary Fellows, Life Fellows or Benefactors shall be by the Board of Governors at any regular or special meeting of the board.

SEC. 2. Election shall be by secret ballot, and three negative votes shall be sufficient to reject the candidate.

ARTICLE VII.

DISCIPLINE.

SECTION 1. The Board of Governors may censure, or suspend, or drop, or expel any member for cause.

SEC. 2. No action for discipline against a member shall be taken before giving the accused a notice of at least one week before the impending action, and an opportunity to appear before the Board and present evidence in his own behalf.

A vote of three-fourths of the Governors present (and in no event less than eight (8) Governors) shall be necessary to censure, or suspend, or drop, or expel, a member. Such action may be taken only at a meeting of the Board regularly called in accordance with the By-Laws.

ARTICLE VIII.

AMENDMENT.

The articles of this Constitution may be amended only at an annual meeting by an affirmative vote of three-fifths of the Fellows of the Institute.

Amendments may be proposed by any member entitled to vote. Notice of a proposed amendment must be presented at a regular or special meeting of the Institute at least one month before the date when final action thereon is to be taken, and must then be referred to the Board of Governors. The Board shall then send a printed copy of the proposed amendment to each Fellow at his last given address, and shall also have the same printed on the announcement of the meeting at which the vote is to be taken.

BY-LAWS

ARTICLE I.

MEETINGS.

SECTION 1. The annual meeting of the Institute shall be held on the first Tuesday in December in each year. At least fifteen (15) days, and not more than thirty (30) days, prior to such meeting the Secretary shall mail to each Fellow, at his last known address, a notice setting forth the time and place, when and where such meeting is to be held. At each annual meeting of the Institute,

three (3) members of the Board of Governors shall be elected; the officers of the Institute shall make full reports of all matters pertaining to the respective officers, showing the particulars of the work of the Institute during the year, and showing, as nearly as posible, the condition of the Institute at the time of such meeting; and such other business may be transacted as may be legally brought before the meeting for its action.

SEC. 2. A special meeting of the Institute may be called at any time by five (5) Governors, by filing with the Chairman a written call, stating the object of the desired meeting, or by the Chairman of his own motion. Immediately upon the filing of such written call, or upon his own motion, the Chairman shall direct the Secretary to mail, and the Secretary shall mail to each Fellow, at his last known address, a notice of such special meeting stating the place and time thereof which place and time shall be fixed by the secretary, the time to be not less than ten (10) nor more than twenty (20) days from the date of the mailing of such notice, and also stating the object for which such meeting is called. No business not germane to the special object mentioned in such call shall be transacted at such special meeting.

SEC. 3. A quorum shall be deemed to be present at any meeting of the Institute when twenty (20) or more members entitled to vote are present.

SEC. 4. Any meeting of the Institute at which less than a quorum is present, may be adjourned my those present from time to time until a quorum shall be obtained, and it shall not be necessary to give notice of such adjournment to any of the members.

SEC. 5. The annual meeting of the Board of Governors shall be held within eight (8) days after the adjournment of each annual meeting of the Institute, at which meeting of the Board the officers for the ensuing year shall be elected and such other business shall be done as may properly come before such a meeting.

SEC. 6. Special meetings of the Board of Governors may be held on not less than three (3) days' notice of the time and place thereof, given to each Governor in person or by mail. Such notice may be given by the Chairman or shall be given by the Secretary when requested by the Chairman or when thereunto requested by five (5) members of the Board of Governors.

SEC. 7. A majority of the Board of Governors shall constitute a quorum for the transaction of business at any meeting of the Board duly called.

SEC. 8. Any meeting of the Board of Governors at which less than a quorum is present may be adjourned by those present from time to time until a quorum shall be obtained and it shall not be necesary to give notice of such adjournment to any of the Governors.

SEC. 9. Notice shall not be necessary to the validity of any meeting of the Institute at which all the Fellows are present. Nor shall any notice be necessary to the validity of any Governors' meeting at which all Governors are present. When a quorum has not been present at a meeting of the Board of Governors, the actions of the meeting shall be valid even though notice thereof has been given, if the Governors not present shall, in writing, on the margin of the record of such meeting, waive notice thereof.

SEC. 10. Any meeting of the Institute and any of the Board of Governors after having duly convened and having proceeded to business, may be adjourned from day to day; and it shall not be necessary to give notice of such adjournment to any member or Governor whatsoever.

ARTICLE II.

DUTIES OF OFFICERS.

SECTION 1. The duties of the President shall be to preside at the meetings of the Institute. At the annual meeting next after his election he shall deliver an address.

SEC. 2. The Vice-President shall discharge the duties of the President when the President is absent or unable to act.

SEC. 3. The Chairman of the Board of Governors shall preside at the meetings of the Board.

He shall exercise a general supervision over the affairs and the business of the corporation, and shall execute in the name of the Corporation (having been

first thereunto authorized by the Board of Governors) all deeds, bonds and other contracts of the Corporation.

The Board may delegate to the Chairman all its powers, provided, however, that it may not delegate to him its power to elect members of the Institute or the Board, and provided further that it may not delegate to him the power of expending money or disposing of any property of the Institute without the previous regularly authorized approval of the Board.

He shall have authority to call meetings of the Board on his own motion, and must call them upon written request signed by five members of the Board or twenty Fellows.

SEC. 4. The duties of the Secretary shall be as follows: He shall be custodian of the seal of the Institute and shall attest the same whenever used; he shall cause full and acurate records of all meetings of the Institute and of the Board of Governors to be transcribed into the Record Book of the Institute over his signature; he shall give due notice of all meetings of the Institute and of the Board of Governors; he shall join the Chairman in executing all deeds, bonds and other contracts of the Institute and shall affix the seal of the Institute to all such instruments and shall safely keep all books, documents and papers of the Institute other than those relating to its fiscal affairs.

SEC. 5. The duties of the Treasurer shall be as follows: He shall receive and receipt for all funds of the Institute and shall deposit them in the name and to the credit of the Institute in such bank or banks as the Board of Governors may designate, or in the absence of such designation, as he may think proper; he shall sign, in the name of the Institute, all checks and drafts upon the bank account or bank accounts of the Institute *provided* that the Board of Governors by resolution may direct all checks or drafts of the Institute to be countersigned by some officer of the Institute to be appointed by the Board of Governors in addition to the Treasurer; he shall, out of the funds of the Institute, make such payments, and only such as shall first have received the approval of the Board of Governors, or of some person or persons authorized by the Board of Governors to give such approval; he shall make no payments except upon proper vouchers and he shall cause all vouchers for payments by him out of the funds of the Institute to be properly filed and preserved; he shall cause full and complete books of account of the business of the Institute to be kept in proper form so that the financial condition of the Institute may at all times be readily ascertained therefrom. He shall give a bond which shall be approved by the Board of Governors, and his accounts shall be audited annually by an auditor or accountant designated by the Board.

ARTICLE III.

MEMBERS.

SECTION 1. The Board of Governors may fix from time to time the number of Fellows, Honorary Fellows, Life Fellows, Associates, and Benefactors.

Candidates whose names have been favorably acted upon by the Board of Governors shall become members of the Institute only after they shall have complied with all the conditions of membership, including the payment of the admission fee. The election of any candidate shall be void if he fails to pay his admission fee, or to comply with the other requirements of admission within thirty (30) days after notice of election is mailed, addressed to him at the place given as his residence on his proposal for membership.

Each candidate for membership of any character shall be proposed by a Fellow, and the proposal shall be seconded by two (2) Fellows of the Institute. The proposal shall be upon a printed form of the Institute, and shall be accompanied by such information from the proposers as will enable the Board of Governors to judge satisfactorily as to the fitness of the candidate, the form of such application to be determined by the Board of Governors.

SEC. 2. The Board of Governors may make such rules for its government in passing upon candidates as it sees fit, provided, however, that only such candidates as have been acted upon by the Committee on Membership shall be presented to the Board for election, and

provided that three negative votes shall be sufficient to reject a candidate.

SEC. 3. No candidate who has been rejected shall again be proposed within twelve months following the date of such rejection.

SEC. 4. Every original and every new Fellow and all Associates shall sign the Constitution and By-Laws of the Institute in token of his or her assent and agreement to be bound by the Constitution and By-Laws, which shall at all times constitute a binding contract between the members so signing.

SEC. 5. Every member on election to and completion of membership shall be entitled to a copy of the Constitution and By-Laws of the Institute.

SEC. 6. Any member who has complied with the Constitution and By-Laws may resign his membership by presenting a communication to that effect to the Board of Governors, but no resignation shall be valid until acted on by the Board. No resignation of any member shall be accepted while his dues are in arrears.

SEC. 7. Any Fellow moving his residence to a point more than fifty (50) miles from the center of Chicago shall be entitled to change his Fellowship and become an Associate on a written application for such change to the Board of Governors.

Fellows and Associates removing to a distance greater than 100 miles from Chicago, may, upon vote of the Board of Governors, be carried on the roll as Fellows, and receive all notices of meetings and copies of transactions.

They shall be exempt from the payment of all dues. In event of dissolution of the Association, they shall not share in the distribution of the assets.

ARTICLE IV.

ELECTION OF GOVERNORS

SECTION 1. At least thirty (30) days previous to the annual meeting, the Board of Governors shall nominate three (3) Fellows for positions on the Board, to be voted on at the annual meeting of the Institute, and shall announce such nomination by a printed notice to all the Fellows.

SEC. 2. The Secretary shall cause the names of all the nominees to be printed on a single slip or ballot, one copy of which, with a copy of this By-Law, shall be mailed to each Fellow with the notice of the election and of the annual meeting.

SEC. 3. Other nominations for these positions may be made by application of fifteen (15) Fellows to the Board of Govenors at least ten (10) days before the date of annual election. If such other nominations shall be made the Secretary shall mail to each Fellow a new ballot showing the names of all nominees, and also showing which nominees are those proposed by the Board.

SEC. 4. The election shall be by ballot deposited in person between the hours of 7 : 00 and 9 : 00 p. m., under the direction of three (3) tellers previously appointed by the Board of Governors, and the three (3) candidates receiving the greatest number of votes shall be deemed elected as Governors.

SEC. 5. No Fellow who is in arrears or whose dues have not been paid, and no Fellow, Life Fellow or Benefactor who is under suspension, shall be entitled to vote or be eligible for office.

ARTICLE V.

COMMITTEES.

The Board of Governors may appoint such standing and special committees and delegate to any of them such of its powers as it sees fit. It shall appoint from its own members a Committee on Membership of five (5). The Committee on Membership shall have power to propose members on its own motion as well as to pass upon candidates proposed by the Fellows. A majority vote of the Committe on Membership shall be necessary to act upon a candidate. Membership in all of these Committees shall expire at the next succeeding annual meeting of the Board of Governors.

ARTICLE VI.

FEES AND DUES

SECTION 1. The admission fee for Fellows shall be $100.

SEC. 2. The admission fee for Associates shall be $50.

SEC. 3. The annual dues of Fellows shall be $25.

SEC. 4. The annual dues of Associates shall be $10.

SEC. 5. No one can become a Fellow or Associate until the corresponding admission fee is paid.

SEC. 6. If the dues of any Fellow remain unpaid for a period of three months after the beginning of the fiscal year, notice shall be sent to such member that if such default continues an additional nine months, he will be dropped from membership. If said dues are not paid within the fiscal year, said Fellow shall be droped from membership without further action on the part of the Board, and can only be reinstated by the payment of back dues and special vote of the Board.

ARTICLE VII.

MEMBERSHIP.

SECTION 1. Physicians or persons engaged in scientific pursuits allied to medicine who are engaged in teaching or research, or like pursuits, and whose income is derived from such pursuits. and who, in the estimation of the Board of Governors, are entitled to this especial consideration, may become Fellows upon the payment of an admission fee of $25. and shall pay annual dues of $5.

SEC. 2. Honorary Fellows, Life Fellows and Benefactors shall be exempt from admission fees and from the payment of annual dues, but they shall be subject in all other respects to the obligations and shall possess all the privileges of Associates. Life Fellows and Benefactors shall have the same rights and privileges in all respects as Fellows.

SEC. 3. Any member of the Institute who under the special provisions of this Article has entered the Institute with an admission fee less than that of Fellows and who has paid dues less than those of Fellows, shall become a Fellow when the conditions of these special provisions cease to exist and thereupon shall pay an extra admission fee equal to the difference between the admission fee which he originally paid and that prescribed for Fellows, and thereafter shall pay the annual dues of Fellows. The Board of Governors may direct any such members to qualify as a Fellow when in its judgment the conditions of said special provisions are no longer applicable to said member.

SEC. 4. Any member of the Institute who shall have reached the age of 70 years, and shall have been a member continuously since its organization, or for a period of 25 years, shall have all the privileges of the membership which he therefore enjoyed, but shall be exempt from the payment of dues.

ARTICLE VIII.

AMENDMENTS

These By-Laws, or any of them, may, at any annual meeting or adjourned annual meeting and not otherwise, be altered, amended, or repealed by the affirmative vote of at least two-thirds in number of the Fellows present at the meeting.

Notice of a proposed amendment must be presented at a regular or special meeting of the Institute at least one (1) month before date when final action thereon is to be taken, and must then be referred to the Board of Governors. The Board shall then send a printed copy of the proposed amendment to each Fellow at his last given address and shall also have the same printed on the announcement of the meeting at which the vote is to be taken.

ARTICLE IX.

THE CORPORATE SEAL OF THE INSTITUTE.

The corporate seal of the Institute shall be a die in circular form upon which shall apear the following words: Institute of Medicine of Chicago—Corporate Seal.

THE PATIENT HIMSELF

HUGH T. PATRICK

President's Address
Dec. 1, 1919

Among the vices of advancing years are carping criticism, garrulity and needless admonition. To all of these I plead guilty and so can only beg your indulgence while I say a few things that I think should be said, knowing that I say them poorly and that I add nothing to our store of knowledge.

My theme is that much neglected individual, the patient himself. Concerning his organs and their functions, we have numberless tomes. Concerning the diseases that attack his parts, we have whole libraries. Concerning the various ways of cutting him open and sewing him up, there are several six-foot shelves. For the manifold instruments, machines and appliances of our armamentarium, an extensive congeries of industries is in constant operation. Indeed, some of us are so used to practicing medicine by machinery that the cortical cell bids fair to shrink into sterile desuetude. But of the patient himself — the man, the woman, the child — relatively little is thought or written.

THE PATIENT ABOVE THE EYEBROWS

What do I mean by the patient himself? I mean what we mean when we speak of our friend, our enemy, our son, our daughter. We like a man because he is sensible, kind or entertaining; dislike him because he is selfish, irritable or pessimistic. So do we admire or despise because of certain mental, not physical, qualities: traits that reside above the eyebrows. Our atttitude depends on the individual's personality: the biggest thing to us and to him. It is more important than his kidneys and his liver, and its disorders are as momentous to him and to society as is disease of his organs. His personality is what he is — the man himself; and he is the sum of all his tendencies and experiences; his desires, aversions, affections, hates, passions, inhibitions, appetites, reflections and knowledge. The tendencies are few and simple, the experiences myriad. A little thought shows that most of this experience has been in the form of conflicts. From the beginning, life is a conflict: an effort to live and be happy — that is to say,

an effort to adapt ourselves to the conditions under which we must live. The struggle between what we consciously or unconsciously wish to do, and what the present state of society requires us to do begins in infancy and never stops. Very early the normal child learns that certain perfectly natural functions may not be fulfilled in a completely natural way. He may not urinate in the parlor, nor appropriate anything he happens to see. As we grow older, these conflicts become more complex and more acute. Some of us come out of them pretty much to the satisfaction of ourselves and our neighbors. We are the happy, the well and the successful. Some of us are unable to make the adjustment. We, then, are the unhappy, the ill or the unsuccessful. Now, as every one of us has these conflicts and has them all the time, it does not take much perspicacity to see that there are many defeats. Occasionally one comes out of the conflict a thief, a tramp, a pauper, an invalid. Probably one does not think of petty larceny, constipation and eye strain in the same terms; but they may be equally due to social inadaptability. Each is the reaction to a difficult situation.

THE RESULTS OF MALADAPTATION

The whole question of health is one of adaptation or adaptability. We have typhoid fever either because individually we are still vulnerable to the typhoid germ, or because as a community we have failed successfully to combat it. Some of us have neuroses or psychoses because we are unable successfully to harmonize with our environment — *and for no other reason.* Often this fact is overlooked. What has social inadequacy to do with the practice of medicine? *A great deal,* because it starts a multiplicity of symptoms which the patient expects the physician to relieve. To speak of the hyperacidity and gastric distress of financial insufficiency, the dysmenorrhea of domestic disharmony and the tachycardia of industrial futility may sound incongruous, but sometimes that is what they are.

An easy approach to consideration of the neuroses as a result of maladaptation, that is to say, as the outcome of a conflict, is by way of the war neuroses because there the conflict is so apparent. A war neurosis, grossly miscalled shell shock, is a means of, let us say, getting out of the front line trenches. The soldier can no longer stand the bursting shells, the falling parapets, the horrible sights and the imminent danger of death. But army discipline and morale, personal honor, pride, ideals make running away impossible. A neurosis makes

it possible. So does loss of an arm. If he loses an arm, the soldier doesn't have a neurosis. A neurosis is no fun, but it is a great deal better than the trenches.

Peace neuroses are just the same. They are a way out of trouble or around an obstacle; a way selected more or less unconsciously. If one cannot remove an obstacle from his path and cannot surmount it, he goes around. Perhaps he *can* push it away, or *can* surmount it; but he *prefers* to go around. For our patients, the way around is often insomnia, "nervous breakdown," backache, dysmenorrhea, asthenopia, indigestion, headache, abdominal pain, dyspareunia, impotence, exhaustion, palpitation and many other things for which medicines are given and operations performed.

As already indicated, a neurosis is by no means the only avenue of escape from an intolerable or uncomfortable situation. Some ways are much simpler. The man who, when tired of his job and dissatisfied with his wife, stops work, gets drunk and beats up his connubial partner, does not develop a neurosis from those particular troubles. He doesn't have to. But he is just the one to get a lame back or sore feet in the army, where he can't escape by the simpler way.

An intelligent and pleasing woman was dissatisfied with her town and her husband. She referred to the former as "a piffling little place," and said of the latter, "He gives me no satisfaction." What was the solution? Recently she spent four months in New York, and with bright eyes and a pleased smile said, "You bet I had satisfaction there." Last winter she visited Los Angeles with the same gratification. Did she have a neurosis? Why should she? There was absolutely no conflict. She was as simple and direct as a child.

Contrast the following:

A woman of 34 years complained of daily headache, poor sleep, ready exhaustion, some dyspnea on exertion, poor appetite and constipation. With considerable pains, I ascertained that she too was dissatisfied with her husband and with her social and financial position. She could not adjust herself to conditions as they were, and she could not change them. Her ideals and training did not allow the simple means of escape adopted by the other. Instead of deliberately going to New York and California, she subconsciously went to headache and insomnia.

NEUROSIS AS DEFENSE REACTION

In short, the neurotic is an individual in trouble with no easy and direct means of escape. A neurosis is a defense reaction, a means of escape; a psychologic dugout in which to hide. That the difficulty may be imaginary, the patient fleeing from a ghost, does not alter the situation. His efforts to adjust his appetites and desires to the

demands of convention, society, the herd are the same as ours. He attempts to dodge defeat and to shift responsibility for lack of success as do we whom a lenient society calls normal. Because he played so poorly, an irascible golfer first threw his bag of clubs and then his caddie into the creek. Very, very often the nervously inadequate person unconsciously shifts the responsibility to some bodily trouble, when he naturally comes into the physician's domain. And too, too often the physician takes his complaint at its face value. Sometimes the literalness of physicians is equal to that of religious fanatics. Once I examined a justly celebrated clergyman who was in a state of profound delusional melancholia, in consequence of which he falsely accused himself of sundry grave sins. Having recovered, he was tried by a church tribunal and dismissed from the ministry because of these self accusations of a disordered mind. Such superficiality and narrowness makes a physician smile. But compare the following:

A young man brought to me his wife, who at various medical hands had received sundry powders and potions for insomnia, nervousness and loss of appetite. After a bit of questioning, I sent the husband on an errand. As the door closed behind him I said, "Now, quick, tell me what's the matter." The startled wife then told me that their young priest, a close friend of the husband, was almost daily assailing her virtue, and that she was quite distracted between fear that she might yield and fear to tell her husband.

And the following:

A woman of 50 years was having a prolonged rest cure because of general nervousness, mental depression, "exhaustion," and insomnia. She appeared to be very weak, and walked across the room with difficulty. A bit of direct questioning revealed that she was intensely afraid of a stroke, and that this fear was based on tinnitus, which she expressed as a "noise in the head." This to her meant cerebral calamity: a stroke, paralysis, death. When the simple situation was explained to her she got up and went to the coast of Maine for a holiday.

Would these medical examples make an ecclesiastic smile? The following incident is not unusual:

Many years ago, only with uncomfortable persistence did I dissuade a well-known surgeon (since deceased) from performing a gastro-enterostomy on his wife. He insisted that she never could be well until operated on. But I knew of grave emotional stress of which he was partly ignorant and which he partly ignored. With the mental adjustment which came about in a couple of years, all abdominal symptoms disappeared, and she has continued well.

How many of us constantly keep in mind that we, the acme of civilization and culture, have every instinct and passion of the caveman? Are we always alert for the ever present emotional-ideational-

intellectual conflict? And do we recognize its importance? To repeat: The product of these conflicts is WE — the patient himself. And in the vast and intricate complexity of modern life, the name of the conflicts is legion. Neurotics are just as different as physicians, and for as many different reasons. Consequently, investigation in many directions is necessary. Here laziness, carelessness and false modesty on the part of the physician have no place. I should not like to say, even if I knew, how often to my question "Did you tell all this to all these other doctors?" the reply has been "No, they didn't ask me."

THE SEXUAL ELEMENT

And here I venture a direct word on sex matters. Without following the self-styled psychanalysts in tracing practically all psychoneuroses to a sexual origin, without even discussing their tenets, I wish definitely to state that something relating to matters sexual has a great deal to do with starting many nervous disorders. Aside from the demonstration of experience, a little reflection will show that this is reasonable. In the present state of society, practically every individual between early childhood and presenility has sexual problems and conflicts. In the solution of the problems and disposition of the conflicts, generally he has the assistance of neither publicity nor knowledge. On the contrary, he is handicapped by ignorance, superstition and isolation. All the conditions are there for the development of fear, shame, remorse, guilt, resentment, a feeling of inadequacy or impotence; the most painful emotions, plus secretiveness. Who would not escape from them by way of a neurosis, very distressing but with none of the tragedy of the other forms of suffering? Thousands of soldiers escaped from the shell torn trenches, that is, from their intolerable emotions, by way of a psychoneurosis. Millions of us have tried to escape from other tearing emotions by means of so-called functional nervous disorder. Hence, whatever our decision as to the psychology of sex, in the case of the individual patient there is but one answer: sufficient investigation, proper instruction, and counsel based on adequate understanding.

But I do venture to add that, in my opinion, to express love of power, money and ease; fear of pain and death; the satisfaction of food, delights of the eye and ear; the disappointment of failure, the pleasure of work well done, all in terms of sex—howsoever sublimated —is to express a narrow conception of *Homo sapiens*. And I also

believe that in the vast majority of cases, the exhaustive and intricate corkscrewing methods of the freudians are unnecessary. Sometimes they are harmful.

DIAGNOSES THAT FALL SHORT

Our medical affinity seems to be the concrete and tangible. Organic abnormality is the most facial explanation of disorder. Given almost any complaint, if the patient reveals undoubted organic disease, our tendency is to stop there. When shall we learn that a prolapsed kidney or stomach may be as good as normal, a valvular lesion innocuous, a urethral stricture of small importance, a deviated septum symptomless, and a torn cervix not even a cosmetic offense? But prolonged fear, disappointment, resentment, anxiety, regret, perplexity are never symptomless. The physician's wife, mentioned above, undoubtedly had enteroptosis; but that did not cause the trouble. The following is a common type:

> A middle-aged woman had been operated on for ruptured perineum, rectocele and "ulcer of the womb"; later, for hemorrhoids and laceration of the cervix. Still later, she had a curettage, and then the ovaries and tubes were taken out. Finally a hernia, a relic of one of the previous operations, was repaired.

No very exhaustive investigation was required to show that this patient never had been physically disabled, but that she always had been intellectually and temperamentally absolutely unequal to life's demands. Each operation was only an additional urge into physical invalidism as an escape from the toil and responsibilities that fell to her lot. That such treatment tends to perpetuate the trouble is obvious. If dysmenorrhea and pelvic pain are really a recourse from laborious housekeeping, ventrifixation fixes the mental attitude of the patient. And the next operation for adhesions makes her more adherent to her disability.

When a women dates her symptoms from marriage or childbirth, it behooves the physician to look for the presence of discontent, unhappiness and fear. A diagnosis of pelvic disease may have to be changed to mother-in-law, which often makes a more or less inadequate daughter-in-law. When a man is disabled by an organic disease or abnormality that apparently doesn't measure up to the disability, one should take the precaution to look for the neurosis which really makes the trouble. A simple arthritis, with which some people would happily limp through life, makes others useless. Why? Because there is

something back of the arthritis; something the matter with the patient himself. While the clinical picture may be made up of symptoms strictly organic plus others purely functional, the latter may be by far the more important, even though the former are more salient.

EFFECTS OF FEAR

Elsewhere,[1] I have tried to emphasize the importance of recognizing fear. One might think that if a patient were afraid he would know it and tell of it. Neither may be the case. That one may be sick from fear and not be aware that he is afraid is certainly true. And "to deny fear seems to be almost as instinctive as that emotion itself."[1] That is to say, the physician must not wait for the avowal: he must dig it out. This is especially true of that exceedingly common apprehension, the fear of losing the mind. Patients will carry this fear for years and never mention it. A very common way of consciously or unconsciously dissembling fear is to complain of the symptom which is the basis or the result of the particular fear. The patient bitterly complains of headache. But the real distress is not the headache (often it isn't a pain at all), but the idea that the headache means insanity or a stroke. Abdominal distress may be trifling, but it is disabling because to the patient it signifies cancer. But he doesn't say so. He hardly knows that it is so. He doesn't wish constantly to be afraid of insanity or cancer; he prefers to have headache or nausea. How can one successfully treat such a headache or stomachache without becoming acquainted with the patient himself?

FREQUENCY OF MILD MELANCHOLIA

One other very practical aspect of the real patient, the patient above the eyebrows, I must at least mention: the frequency of unrecognized mild melancholia. Instinctively, these patients hide their feelings of uselessness and hopelessness, their self reproach and fear of insanity. They complain of what to them seems to be the cause of their ill feeling, and generally this is some bodily complaint. Headache, insomnia, indigestion, constipation, biliousness; exhaustion from overwork, worry or sexual irregularities; leukorrhea, loss of memory and pelvic distress are among the more common. And the literal physician overlooks the disorder of the personality. The result is useless or

[1] Patrick, H. T.: The Factor of Fear in Nervous Cases, J. A. M. A., 1916, 67, p. 180.

harmful treatment. This is bad enough. What is worse, the patient is given every chance to commit suicide — which he rather frequently does. In Chicago there are more than 600 suicides a year, and I am quite sure that fully 400 of these are due to melancholia — every one of them preventable.

EFFECT OF DISTURBING EXPERIENCES

The relations of past experience to present conduct are most complex. Our feelings and behavior today are the result of myriad experiences, most of them forgotten, and still more not in our awareness at any given time. No man can trace all the steps that have led him to be a Republican, or to dislike a certain person. Why does Miss X delight in ice cream, and abominate pork chops? It didn't just happen. There are reasons. Of four men in trouble, one prays, one gets drunk, one has a fit and one has a headache. Why? That is for us to find out. Generally, it can be done. Not always.

Clinically, the relation of a pathogenic experience to consciousness is generally one of two, with no definite line of division. First, the patient remembers perfectly well the (generally unpleasant) experience, but has no idea that it has anything to do with his present trouble. Second, the disturbing episode has been quite forgotten and is brought back into consciousness only by some unusual stimulus or mental state. Obviously, it may happen that we cannot bring it back at all. To illustrate the first type:

A young traveling man was unable to eat in restaurants because of intense feeling of prostration and oppression, palpitation, etc. He had not in any degree forgotten that a few months before consulting me, he had been taken very ill while dining in a restaurant, had nearly fainted, and had liberally distributed vomitus over the floor before he could get out. But apparently, a connection between the causative disagreeable episode and the neurosis never had occurred to him, and information of the illness was not volunteered. It was elicited by leading questions.

Another example:

A middle-aged, happily married woman complained of nervousness, insomnia, mental depression, intense dislike of social intercourse, even with good friends, and intense agoraphobia. Painstaking inquiry for more than two hours, evidently with the cooperation of the patient, failed to elicit a cause. Only after the analysis of two dreams by Dr. Lewis J. Pollock, my assistant at that time, did we learn of events in her childhood and youth causing poignant shame and self reproach that were clearly the cause of her disorder. These experiences

she had not forgotten; but their relation to her present complaints had never occurred to her, the subject was distasteful, and instinctively, scarcely deliberately, she had suppressed the facts.

An example of the second type:

A young married woman had so-called vaginismus to a degree entirely preventing intercourse. No local cause could be found. The patient neither feared nor objected to the nuptial embrace; indeed, she was most anxious to be a complete wife and an early mother. It was only after many questions and the awakening of many associations that she recalled two not very striking experiences when she was about 11 years old. Aside from temperament, these were the prime cause of her disorder; but apparently for years she had not consciously thought of them.

NEED OF APPROPRIATE TREATMENT

A good many years ago, Möbius described akinesia algera, paralysis from pain; the patient does not move because it hurts to move. When we come to therapeutics for the patient himself, many of us have a sort of amblyopia algera. We do not see because it is uncomfortable to see. It is much more comfortable to say, "nothing to it," "just a nervous crank" and do nothing, than it is to realize that here is a pathologic condition, obscure, may be complex, that must be laboriously worked out. So we naturally go blind, see nothing and do nothing. Probably every physician makes an effort to regulate the bowels. How many of us make an effort to regulate emotional and intellectual movements? But intestinal stasis is vastly to be preferred to intellectual stagnation: so-called autointoxication is not half so lethal as disintegrating emotions.

To state it another way, we must first have a just conception of the nature of the trouble and then institute *appropriate* treatment. Nowadays few ovaries are removed for dizziness and indigestion, but the "rest cure" is applied about as heedlessly as was formerly oophorectomy. Confinement to bed, isolation, forced feeding and massage for perturbations of the personality may be compared to a linseed poultice for pain in the belly. Occasionally the cataplasm suffices, but treatment of the cause is to be preferred. Equally, we should treat the cause of neurotic manifestations. Who would prescribe a pill for vagrancy or a powder for prostitution? The tramp and the prostitute are recognized as defective, unadaptable to society as now constituted, except on the underworld level. The psychasthenic (nearly always miscalled neurasthenic), the neurotic, the psychotic is a rather similar product. Unadapted to the upper strata of social efficiency, he gravi-

tates to the underworld level of pain, prostration and dyspepsia: the realm of consultation rooms, hospitals and sanatoriums. But I hasten to add that when properly adjusted to his environment, the neurotic may be one of the most efficient, valuable and delightful members of society.

A fine young woman was about to decline marriage because handicapped, even disabled, by what she did not recognize as phobias. For years she had been unable to go down town except in a carriage, and then only for a few minutes. To go alone to a nearby market was out of the question. Deeply religious, she could not go to church alone, and when accompanied, she could sit only near the exit. There were other phobias. A short course of training and reeducation removed the lot, and for about ten years she has been an ideal wife and mother.

A fine young chap of 22, because hypersensitive and hyperconscientious, became depressed and worried over the usual sexual problems of youth to the extent of total disability. The situation was explained to him: in a proper environment, he was carefully guided and was gradually led back to normal activities. In the spring of 1917, he entered the army and served brilliantly thoughout the war.

An unmarried woman of 29, doing office work, for ten years had had attacks of dyspnea and palpitation, great weakness and insomnia. Although she positively and honestly denied that she was afraid of anything, exact questioning showed that she had several intense phobias. She really was ill and had been for ten years. But the trouble was not the heart muscle, it was lack of adjustment to her job, her associations and necessary conditions of living. Fortunately, she married happily, and her bodily complaints all disappeared.

A woman of 32, of the intellectual type, had been an invalid for years. Accurately to describe her symptoms would require a descriptive catalogue. They included "stomach trouble," "rectal trouble," severe headaches, ready exhaustion, tenderness at places over the abdomen and in the pelvis, loss of weight and anemia. She certainly had enteroptosis, with the right kidney far down. One of the greatest surgeons of Chicago thought it best to take out the appendix, fasten up the kidney, ventrifix and curet the uterus. Did all this help? Not a bit. She was sent East for a prolonged rest cure under the greatest master of that procedure, with the same result. She remained the same practically useless martyr, a burden to herself and the despair of her family. Finally, she was induced to take up an active, intellectual and taxing occupation in an environment that fitted her. Presto! The baffling organic disorders, the profound prostration, the disabling pains evaporated. She had found her place, and she has continued to be a busy, exceedingly useful and happy woman.

The following case shows the obverse mechanism:

A young man of ample means, shy and a bit effeminate, retired to a small farm where he raised a few fancy sheep and experimented in crossing flowers —all to his complete satisfaction, and he himself in perfect health. Circumstances forced him into business and the hated city. He developed rebellious stomach trouble, insomnia and headaches, lost considerable weight and frequently his temper.

NATURE OF THE TREATMENT

These illustrations, which might be continued indefinitely and with interesting variations, serve to indicate not only that the neuropath may be useful but also what sort of treatment he should have. Very simply stated, the object is so to mold the patient that he will fit his environment, and so to arrange the environment or so to place the patient that the environment fits him. Sometimes it cannot be done. Our laws and customs contain fragments from the dark ages and more primitive eras. So do we. Some of us belong to the period about 100 A. D. For such, transplantation to the present epoch is difficult. A few of us belong in the stone age, and we cannot live in the captivity of modern civilization without falling ill. Perhaps occasionally one is 500 years ahead of his time. If so, he has a hard life, and probably is a failure, judged by our standards.

In assisting to adjust a patient to necessary conditions, frequently we have to show him that he can do things that he says he cannot do. That is his way of expressing his great reluctance to do or fear of doing something necessary for his health. Demonstration discounts admonition. He should be given an understanding of his situation; but simply telling him is not enough. We must demonstrate to him that he can eat turnips or walk a mile or sleep without a hypnotic, or go without a headache powder.

Let me again emphasize that the headache or the pain in the legs or indigestion is simply a means of escape from something for which the patient feels himself inadequate, or really is inadequate. Our job is to make him equal to the task he is trying to escape or so modify the task that he can perform it, or give him another which he can do with satisfaction. To say, "Don't worry" or "Why worry?" or "That headache isn't in the least serious" is not enough. The unwholesome ideas, the distressing disorder, can be driven out only by wholesome satisfactory ideas, which in the vast majority of cases means a satisfying occupation, a something which makes life taste good.

THE OUTCOME

And for our encouragement, we may remember that the temperamental individual who is confused and discouraged by life's perplexities and takes refuge in physical disabilities is, when rightly placed, likely to be the finest enthusiast and the most glowing optimist. Just as he is

dominated and defeated by a depressing idea, so is he exhilerated and activated by sanguine ideas. Some of the greatest and most beautiful work of all time has been done by these men and women who are too much controlled by their emotions, too sensitive to the jars of a battling society, too unstable to carry the gross burdens of a materialistic world. Ours is the task, then, to strengthen their intellectual control, to toughen their shrinking sensibilities, and to modify their burdens. Thus may we, too, add to the sum total of human health, happiness and progress.

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NEWER ASPECTS OF NUTRITION

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Nov. 24, 1919

Much has been accomplished in developing preventive medicine as a science, but activity in this field has in great measure been restricted to attention to the purity of the water supply, to sewage disposal, general sanitation, food inspection and the prevention of food adulteration. It is now well recognized by all progressive public health workers that education of the public in the principles of correct living, and the periodic medical inspection of all persons, notwithstanding the apparently healthy condition of many, constitutes the next, and in many respects the most important, line of advance. Such a plan will go far toward remedying defects before they become serious. Thus the tendency of today is toward doing preventive medical work with the individual as well as with the community.

There is another phase of the problem of prolonging the life and period of productivity of man which is not as yet very popular with the medical profession, but which has aroused the enthusiastic hopes of several investigators who have had the opportunity to make extensive observations of the effect on animals of diets similar in chemical composition. I refer to the prospect of planning the diet of the individual from infancy to old age so as to induce the optimum of nutrition. It has been thoroughly demonstrated that by proper diet much more can be done to promote health and to maintain the characteristics of youth than has been hitherto supposed.

We do not yet know with certainty why it is necessary, as general experience indicates, that man should become senile and die. The studies of Maupas and of Woodruff show that certain lowly organisms are capable of reproducing endlessly without conjugation. They prove that certain types of protoplasm are essentially immortal.

In the higher animals whose bodies are made up of a multitude of cells representing several types of specialization, the problem of nutrition and of eliminating the waste products of metabolism is more complicated than in the simple organisms, and is fraught with greater hazard to the individual. Each of the glandular tissues in these must assume the duty of working for other tissues. The digestive glands must functionate far beyond their own individual needs in order to

prepare food for the other tissues of the body. The kidneys must come into intimate contact with and secrete into the urine the metabolic end-products of a mass of protoplasm a hundred or more times their own bulk, as well as their own. The variable but more or less constant stream of foreign and more or less harmful substances formed in the lower intestine through the agency of micro-organisms must likewise pass through the kidneys. It has long been believed by Metchnikoff and others that the latter factor is one of great significance in causing damage to the tissues of the body and of contributing to early deterioration.

The tendency toward over-fatigue of certain of the more important tissues through the necessity of working for others as well as for themselves cannot be avoided beyond a limited degree. Reduction to a small fraction of the usual degree of injury that may result from the generation of foreign and toxic chemical substances in the digestive tract can, however, now be occomplished.

The adjustment of the protein intake to meet the requirements of the body, and at a level such that any benefits that may result from its stimulating qualities are gained, but not sufficiently high to cause the detriment which all agree results from surfeiting with protein food, doubtless forms one of the important factors in the preservation of vitality and health. There are several factors concerned with the plane of protein intake that we do not well understand, but considerable is now known about this phase of nutrition.

Modern research has shown that the relationships among the inorganic elements that are essential for the normal functioning of protoplasm form a much more important factor in growth and longevity and in consequence well-being than had hitherto been supposed. Even the difference between the calcium, sodium and chlorin contents of certain classes of our most important natural foodstuffs is sufficiently great to determine whether or not growth can take place. Although our knowledge of the details of this important question is still rather meager, some of the more easily regulated ones can be controlled in ordinary practice to the advantage of man and animals.

In the popular mind, the most attractive feature of the subject of nutrition during recent times is the spectacular effect of the lack of a sufficient amount of one or another of at least three chemical substances whose existence was not suspected a few years ago. The dietary deficiency diseases, scurvy, beri-beri and xerophthalmia of a

certain type, result from specific starvation for one or another of these substances. The optimum amount of these substances in the diet cannot be stated in the light of our present knowledge, but the content of each of them in certain of our more important foodstuffs is sufficiently well known to render it possible to plan diets so as to guarantee a reasonable degree of safety.

Animal experimentation has shown that there are great differences in the biologic values of the proteins derived from different sources. This difference depends on the fact that the proteins in different foodstuffs yield varying amounts of the amino-acids or digestion products. If the yields of the several amino-acids is such as to make possible the efficient transformation of food proteins into tissue proteins the proteins have a high value. If, however, one or more of the amino-acids is present in such small amounts as to make it impossible to utilize the more abundant amino-acids, they form the limiting factor that determines the value of the protein in nutrition. Many of these digestion products are indispensable in the diet, since they cannot be synthetically produced within the tissues. In considering the value of a natural foodstuff or of a diet consisting of a variety of substances, the idea of quality of protein enters into the calculations of the dietician of today,

Our knowledge of the great variation in the biologic values of proteins from various sources throws a new light on a possible source of injury to the body tissues. Excessive feeding of proteins is generally held to lay a burden on the organism because of the magnitude of the task of metabolizing the quantity of amino-acids absorbed. From what we know of the intermediate compounds formed in the catabolism of amino-acids, there can be little doubt that some are a physiologic abomination, and dealing with them by the glandular structure is not without a degree of unfavorable effect that in time produces visible alteration in their functional capacity. It seems logical to assume that physiologic well-being will be best promoted by the employment in the diet of proteins so constituted as to be transformable with little waste into tissue proteins.

The best chemical analysis of a foodstuff which the chemist is able to make determines the amounts of protein, carbohydrate (starches and sugars), fats and oils, and mineral salts that it contains. For more than thirteen years it has been known, however, that when a mixture of these substances, each carefully purified, is fed to a young animal the latter cannot grow, or live long. The reason was very difficult to

Explanation of Plate I

Chart 1.—Lot 417 shows the results of restricting young rats to a diet of purified protein, salts, carbohydrate and agar-agar, together with an extract of a natural foodstuff that furnishes the dietary factor, water-soluble B, the substance which prevents beriberi. The diet was complete except for the absence of the fat-soluble A. As a rule, there develops in animals so fed, a type of xerophthalmia, which is due to the lack of the fat-soluble A. When a fat or other natural food rich in cellular structures (as contrasted with reserve food materials), is added to a food mixture of this type, the resulting diet becomes capable of inducing growth.

Lot 418, period 1, shows the curves of body weight of rats fed a diet similar to that described above for lot 417, but differing in that it contained butter fat (fat-soluble A) but lacked the extract of natural foods, and, therefore, contained no water-soluble B. On this diet xerophthalmia does not develop, but the animals ultimately lose muscular control and manifest symptoms suggestive of beriberi in man. Growth is not possible on this diet, but everything which is needed in the diet so far as chemical analysis could show, is present.

These results show the necessity of a biologic analysis of foodstuffs. Growth at once took place when, in period 2, the dietary essential water-soluble B, which is likewise soluble in alcohol, was added to the diet. This dietary factor is abundant in all natural foods. In investigations of the nature of those here described, it is usually added as an alcoholic extract of a natural food.

Lot 419 shows the type of growth curves secured with diets containing both fat-soluble A and water-soluble B, in addition to the long recognized food substances, protein, carbohydrate, fat and a satisfactory supply of the inorganic elements essential for the nutrition of an animal. There is much reason to believe that each of the two unidentified dietary factors A and B contains but a single chemical complex which is physiologically indispensable, and not a group of such substances.

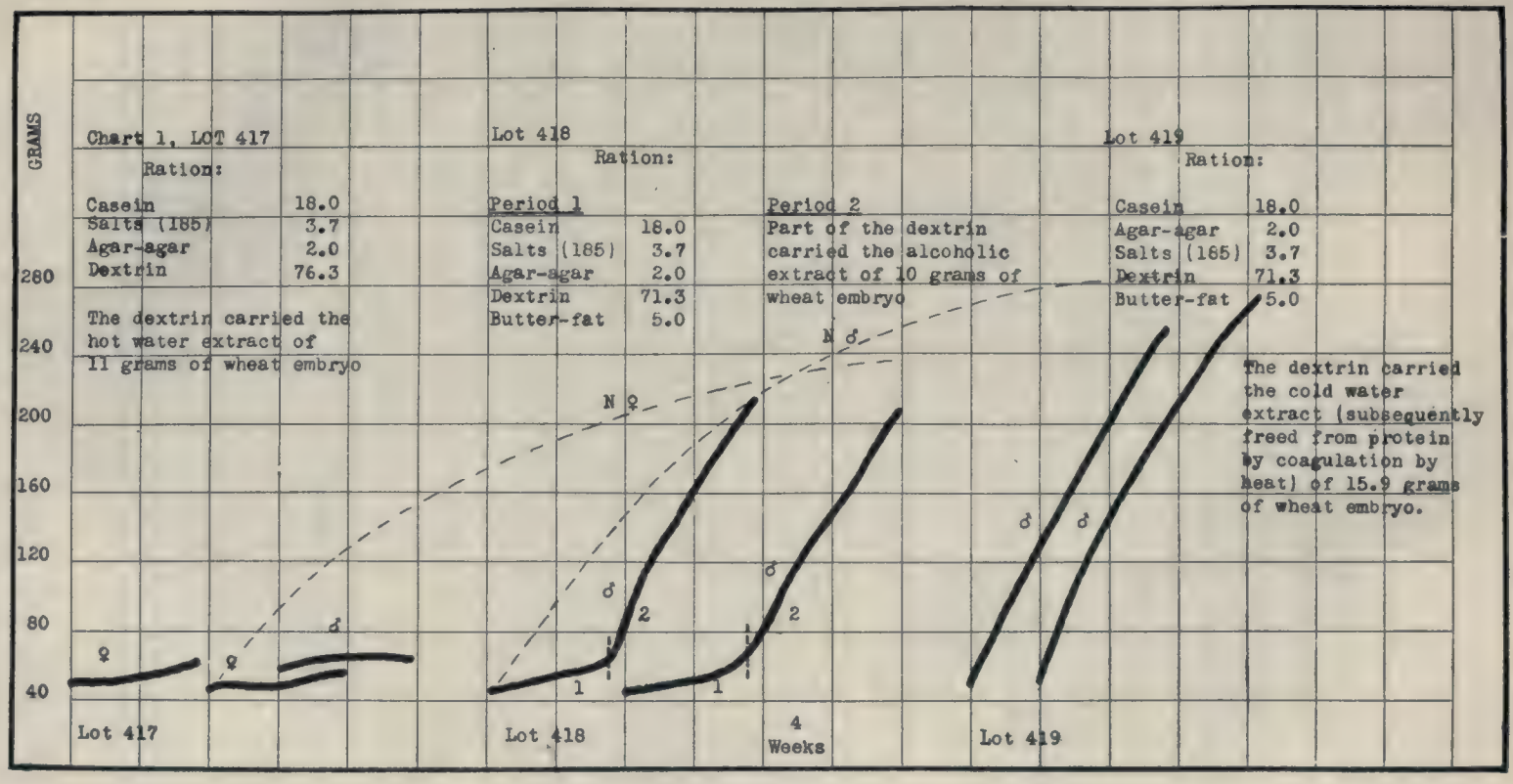
GRAMS
280
240
200
160
120
80
40
Chart 1, LOT 417
Ration:
Casein 18.0
Salts (185) 3.7
Agar-agar 2.0
Dextrin 76.3
The dextrin carried the hot water extract of 11 grams of wheat embryo
Lot 418
Ration:
Period 1
Casein 18.0
Salts (185) 3.7
Agar-agar 2.0
Dextrin 71.3
Butter-fat 5.0
Period 2
Part of the dextrin carried the alcoholic extract of 10 grams of wheat embryo
Lot 419
Ration:
Casein 18.0
Agar-agar 2.0
Salts (185) 3.7
Dextrin 71.3
Butter-fat 5.0
The dextrin carried the cold water extract (subsequently freed from protein by coagulation by heat) of 15.9 grams of wheat embryo.
N ♀
N ♂
♀
♀
♂
♂
♂
♂
♂
1
2
1
2
Lot 417
Lot 418
4 Weeks
Lot 419

PLATE 1

ascertain, for it is due to the lack of certain substances of a moderately unstable nature, the existence of which was not suspected. Certain species of animals, such as the rat, appear to require, in addition to the long recognized dietary complexes, but two of the unidentified dietary essentials. The most common designation of these is perhaps the term "vitamin" which includes fat-soluble A and water-soluble B. No less than twenty-five names have been invented for these substances. Other species of animals, such as man, guinea-pig and monkey, require three, the additional one being called water-soluble C. These terms have been applied provisionally pending the discovery of the chemical natures of these interesting substances. The importance of each of these substances in the diet of the rat is illustrated by the curves in chart 1.

It has been abundantly demonstrated that for satisfactory nutrition the mammal requires nine mineral elements in addition to the essential organic complexes, in order that its diet may be adequate. These are calcium, magnesium, sodium, potassium, chlorin, phosphorus, sulphur, iron and iodin. These can be supplied in the form of inorganic salts except in the case of sulphur, which must be contained in the diet in the form of the sulphurized amino-acid cystine. It is doubtful whether there is an order of relative importance among these, for it appears that all are indispensable. There must be present in the diet either glucose or a carbohydrate which can be converted into glucose in the body. Cane sugar, glucose, beet sugar and the starches serve this purpose.

It seems highly probable that fats and substances closely related chemically to the fats are entirely dispensable in the diet. Up to the present time it has not been found possible to nourish an animal properly with a diet free from this class of compounds because one of the unidentified dietary essentials is associated only with certain fats. Therefore, in working with a diet made up of purified foodstuffs it has been necessary in every case to add one of these fats, not because of the fat itself, but because of the presence of an unknown substance (fat-soluble A) which is contained in it.

It is interesting to consider the distribution of the three unknown substances that the diet must contain. The substance fat-soluble A is found in butter fat and egg yolk fats, and in the fats from the interior of the cells of the glandular organs of animals (e. g., the liver and kidney) in greater abundance than in any other foods. Leaves of plants constitute the next important source. The seeds, tubers and

fleshy roots are all relatively poor in this substance. It has been suggested that among the latter those which contain yellow pigment are richest.

The water-soluble B dietary factor is widely distributed among natural foodstuffs. The only common foods lacking in it are polished rice, the sugars and starches, and the fats and oils from both animal and vegetable sources. Food containing small quantities of it are: white flour, degerminated cornmeal, macaroni, spaghetti, and other products prepared principally from bolted wheat flour. All whole seed products, tubers and fleshy roots, leafy foods, milk and eggs contain it in relative abundance. Muscle cuts of meats are very poor in it, but the glandular organs contain it in abundance.

The water-soluble C is abundant only in fresh vegetables, fruits and fresh milk from cows in pasture. Cooked and dried foods have in great measure lost their peculiar dietary properties with respect to this substance.

The effects of specific starvation from one or another of these three substances are of special interest. Each of them is necessary in the diet in order to prevent the development of a specific syndrome that we call collectively deficiency diseases.

One of these, which is caused by a lack of fat-soluble A in the diet, is characterized by a change in the eyes, in which edema, inflammation, and in some cases perforation, are the most important. Much remains to be learned regarding the histology and pathology of starvation for this dietary complex. Without it growth is impossible, and death soon intervenes. There is much evidence that a lack of a sufficient amount of fat-soluble A is one of the factors associated with the etiology of rickets.

A lack, either relative or absolute, of the second dietary factor of unknown chemical nature, water-soluble B, leads to the development of a condition of polyneuritis which in man is known as beriberi. Paralysis is the most striking general feature of the disease.

The third of the dietary complexes under consideration is that which prevents the development of the syndrome of scurvy. It is the least stable of the three. The antineuritic substance is the most stable.

For several years the three substances just discussed have in the popular mind overshadowed in importance the long recognized dietary essentials. It should be emphasized that there is no basis in fact for considering them any more important than the proteins or than any

one of the essential mineral elements. All are indispensable components of the diet, and are, therefore, of essentially equal importance. Any appraisal of the quality of a diet must include a consideration of the quality and quantity of protein; the content of each of the necessary mineral elements; the content of each of the substances concerned with the etiology of the deficiency diseases, and the availability of its carbohydrates.

After the factors which operate to make a diet complete and satisfactory were appreciated, a series of studies were carried out with a view to determining the nature and extent of the dietary shortcomings of each of the more important of our natural foodstuffs. In the light of these studies it has become possible to make certain generalizations of far-reaching importance in the nutrition of man and animals. On these observations is based a new type of classification of the vegetable foodstuffs depending on the function of the part of the plant from which they are derived.

It has been found that all those parts of plants that have the functions of storage tissues, viz., the seed, tuber and fleshy root, have remarkably similar dietary properties and similar shortcomings. Notwithstanding the great difference between the legume seeds, such as the pea and bean on the one hand and the potato or turnip on the other, they have very nearly the same dietary values in certain respects. All of the cereal grains, legume seeds, tubers and edible roots are deficient in some degree in at least three dietary factors. All contain proteins of relatively poor quality; all contain too little of certain mineral elements, especially calcium, sodium and chlorin, and all are deficient in fat-soluble A. As stated above, there may be a few exceptions to the latter generalization in the case of certain yellow pigmented roots.

The leaf of the plant possesses very different dietary properties from the seed. The palatable leaves are alone a complete food for those types of animals that have digestive tracts sufficiently capacious to enable them to eat a sufficiently large amount to meet their energy requirements. This superiority in dietary properties correlates with the special function of the leaf as contrasted with the storage tissue, such as the seed, tuber or root. The leaf consists of actively functioning protoplasm supported by skeletal tissue. It is the seat of the synthesis of proteins, carbohydrates and fats. It is the seat of active respiration and metabolism. The seed, tuber and fleshy root represent on the other hand packages of reserve food materials, with a few living elements.

In general the structures of the storage tissues do not contain all the complexes necessary for the construction of living protoplasm, and are accordingly incomplete foods.

A similar parallel between function and dietary properties can be drawn in the case of the highly specialized muscle tissue on the one hand and the actively metabolizing glandular tissues on the other. The muscle tissue has dietary properties almost identical with the seed, tuber or root in all respects except its richness in protein. It lacks calcium, sodium and chlorin, fat-soluble A, water-soluble B and water-soluble C. The glandular organs, such as the liver and kidney, are much more complete foods. Indeed, they have all the complexes that are essential for the construction of living tissue, and when supplemented with certain salts, a carbohydrate, such as starch, approximate much more nearly a complete food than would a similar amount of muscle tissue with starch.

Since there are closely similar dietary properties in the storage tissues of plants and of muscle tissue of animals, it should be expected that mixtures of these even in considerable numbers should not form satisfactory diets. In many feeding experiments this has been shown to be the case. Although it is possible for a young animal to grow on a seed, tuber, root and muscle cut of meat diet, its growth is never normal in rate or extent. It will always be stunted, and will fall below the normal standard of performance in reproduction and rearing of young, and in span of life.

Consistently unsatisfactory results have been secured on diets consisting of wheat flour, cornmeal, rice, peas, beans, potato, turnip, beet, rolled oats and round steak. The round steak was included to the extent of 10 per cent. of the dry matter of the diet.

This leads us to a consideration of diets that succeed in the nutrition of animals. In an extensive inquiry, covering 12 years, and based on nearly 4,000 feeding experiments, we have succeeded in nourishing animals in an approximately normal fashion with but 3 types of diets.

It is possible to select carnivorous foods so as to secure a fairly satisfactory diet entirely derived from animal tissues. Young animals cannot grow or long remain in health when restricted to muscle tissue as their sole food. When blood, liver, kidney and other glandular tissues are selected, together with a certain amount of bone substance, the food supply is sufficiently good to lead to normal development.

Muscle tissue must be liberally supplemented with glandular organs to make possible success with the strictly carnivorous diet. The carnivorous diet has been used by man occasionally, the Eskimo and some American Indians being examples.

It has been found possible to supplement the seed, tuber, root and muscle meat type of diet with liberal amounts of the leafy vegetables and secure a fairly satisfactory diet. This requires a liberal supplementing with leaf in order to make good the deficiencies of the remainder of the diet. This type of diet is common among the Orientals.

The third type of successful diet is that derived from cereals, legume seeds, tubers, and fleshy roots, with or without meats, supplemented with liberal amounts of milk. Milk is so constituted as to make good all the deficiencies of the classes of foods just enumerated.

It is so important to appreciate the special qualities of the leafy vegetables and milk that I have been accustomed to designate these as the protective foods. They are protective because they are especially rich in those elements and complexes in which the storage tissues of plants and muscle tissue are poor.

I will now consider the application of the facts discovered through animal experimentation to human problems.

Various attempts have been made to account for the differences in achievement of man in the several parts of the world. Some investigators regard race as the most important factor and believe that certain races are naturally inferior to others. Huntington of Yale University attributes to climate the most important rôle in determining the efficiency of man in the several regions of the world. Numerous authors have emphasized the importance of a satisfactory diet for the maintenance of the health and of physical fitness, which all agree forms the fundamental basis of achievement. No one up to the present time has, however, been able to make a strong case in favor of nutrition as a factor; this is proved by the number of dietary systems and fads which have been offered to the public. While one enthusiast extols the virtues of abstemiousness, another warns against it and points to the high meat consumption of the successful nations of the earth. While thousands of dyspeptics adopt vegetarianism, others explain the remarkable health of centenarians as being due to the bacillus of sour milk. The pronounced difference in the value of a food mixture consisting of cereal products, tubers, roots, legume seeds and steak,

with and without milk, is shown in chart 2. Careful consideration shows that the more advanced peoples of the world are those who live on the vegetable and meat diet supplemented with milk and its products. The second class in respect to advancement and aggressiveness includes those that eat liberally of the leafy vegetables. All strictly carnivorous men live in climates that preclude the development of any high degree of civilization. They have nothing to strive for further than food, shelter and clothing, and do not accumulate much property.

There can be no doubt that there are carnivorous animals such as the lion, tiger and jaguar, that live in the hottest parts of the world, yet represent some of the best examples of physical development in the animal kingdom. Neither the heat, monotony or high temperatures, humidity or aridity can be said to interfere with physical development.

The tiger thrives among the wet estuaries of Bengal, and the jaguar in the hot and sultry forests of Brazil. The lion is equally vigorous on the margin of the desert. We can find no evidence that climate is a factor of any appreciable importance in the development of lower animals so far as physical well-being is concerned.

Huntington has made a very plausible case for climate as the most important factor in determining the efficiency of man in the different regions of the world. He points out that the changes in the condition of the weather so characteristic of the northern parts of the United States and lower Canada in the western hemisphere, and of England, northern France, Holland, southern Germany, etc., are the ideal conditions for stimulating effort, both physical and mental. This assertion he bases on careful observations on the amount of work of several kinds which workers accomplish in climates varying from that of Connecticut to that of Florida. Temperature he finds to be the important factor in determining the aggressiveness and ambition of the individual. The farther south one goes, the more uniformly warm it is, and the more the climate departs from the typical cyclonic stormy type so characteristic of the northern states and of England.

Huntington further correlates the character of the climate of Europe, Asia, Africa, and North and South America, with the state of advancement of their peoples, and finds a remarkable relationship between them. Monotony of climate over long intervals is said to be detrimental to achievement. He eliminates race as an important factor in determining the problem by pointing among other illustrations to the

Explanation of Plate II

Chart 2.—Lot 2,147 received a diet of wheat flour, cornmeal, potatoes, beets, turnips, peas, navy beans and steak.

In the absence of experimental demonstration no one would believe that this food mixture would fail to meet all the needs of a growing animal. The addition of a liberal amount of milk serves, however, to improve this diet in a remarkable degree.

Lot 2,148 was given the same food mixture as lot 2,147, except that 10% of whole milk powder (Merrill-Soule) replaced a part of the potato, peas and beans. The effect of this addition on the growth curve and span of life is indicated by a comparison of the two growth curves in chart 2. These rats each fairly represent a group of six animals in their experimental groups. Certain foods, such as milk and the leafy vegetables, are to be regarded as protective foods because they correct the faults of those common articles that enter freely into the diet of man.

The list of foods in the diet of Lot 2,147 can be combined in a typical menu as follows: broiled steak, baked potatoes, peas, pickled beets, bread, mince pie, coffee. While this menu is, if properly prepared, appetizing and attractive, and affords the extent of variety to which we are accustomed, it is deficient in certain respects, viz.: in the element calcium and in the unknown dietary essential that is most abundant in certain fats but not found in vegetable fats or oils.

This menu can be easily modified by the inclusion of milk to make it a much more satisfactory diet: broiled steak, mashed potatoes, creamed peas, buttered turnips, bread, lemon pie, coffee.

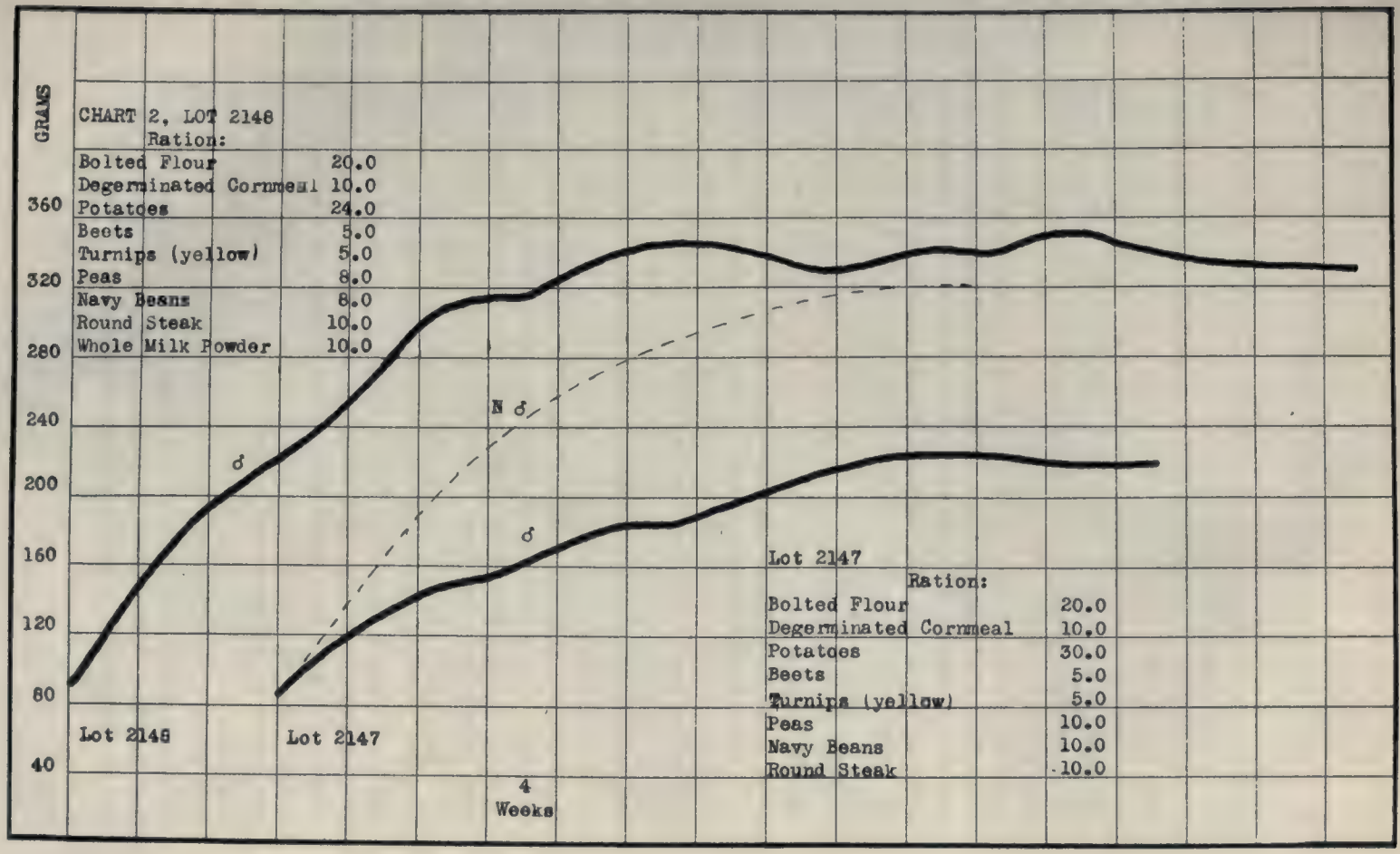
GRAMS
360
320
280
240
200
160
120
80
40
CHART 2, LOT 2148
Ration:
Bolted Flour 20.0
Degerminated Cornmeal 10.0
Potatoes 24.0
Beets 5.0
Turnips (yellow) 5.0
Peas 8.0
Navy Beans 8.0
Round Steak 10.0
Whole Milk Powder 10.0
♂
N ♂
♂
Lot 2147
Ration:
Bolted Flour 20.0
Degerminated Cornmeal 10.0
Potatoes 30.0
Beets 5.0
Turnips (yellow) 5.0
Peas 10.0
Navy Beans 10.0
Round Steak 10.0
Lot 2148
Lot 2147
4
Weeks

PLATE II

condition of the white people of the Bahamas, who are the descendants of virile Southern settlers, as contrasted with that of other loyalists who at the time of the revolution emigrated to Canada. The former have degenerated into "poor whites" who are too proud to work at menial labor in competition with the negro, and too shiftless to compete with him successfully. The latter are among the most prosperous and progressive citizens of one of the finest examples of a commonwealth in the world.

Huntington sees no great hope for the future of civilization in Asia, Africa or South America, because the white man, who is regarded as superior to the other races, degenerates in the enervating climates. The view is held that when the white man migrates to climates less stimulating than those of his original home, he appears to lose both in physical and mental energy. If it is true that under such influence man becomes careless of sanitation and of food, and thus secondarily becomes susceptible to diseases, then indeed there is little reason to hope that the dream of the hygienist can be realized, viz., that the tropics can ultimately be made the abode of a cultured population.

Plausible as is the correlation between climate and civilization which Huntington has constructed, it seems to me that another interpretation can be placed on all the data that he presents, which in the light of what we now know about the effects of diet on health, will come nearer the truth. In order to appreciate the importance of diet on the welfare of nations we should consider for a moment the effects of certain types of faulty nutrition on the life history of experimental animals.

When a full grown animal, such as a rat, is placed on a diet of seeds, tubers, fleshy roots and muscle meats, it begins to hurry through the span of life, developing the characteristics of old age at a rate double or more the rate observed in a well nourished animal. Such animals do not succeed well with the nutrition of their offspring, and die at a fairly early age. The young, if restricted to the diet of the parents, are never their equal physically, have poor success with their young, live a much shorter period than the species is capable of, and are subject to infections and abnormalities in a degree unknown in their ancestors. With each succeeding generation weaklings predominate, and the strain dies out within a few generations.

If we apply to the natives of the Bahamas the test of nutrition, we find that the diet is of such a character as to account for degeneration in considerable degree within the period since the islands were

settled by loyal Tories who were not willing to live under the Stars and Stripes. During this period they have depended for their food supply largely on citrus fruits, pomegranates, pineapples, bananas, melons, yams, potatoes, guinea corn and peas. This list, it will be noted, consists of fruits and other storage tissues of plants. It has been supplemented with a certain amount of animal foods, principally fish, although some muscle meats from mammals have been eaten. This type of diet, it will be remembered, is unsatisfactory for the nutrition of an animal over many generations, and leads to deterioration in the stock. This is the condition found in the Bahamas.

On the other hand, the people of Canada have lived essentially on the same type of diet as that employed in the northern United States. It includes all the products of field and garden with which we are familiar, together with meats in liberal amounts and dairy products in moderate quantities. The latter is the kind of diet that supports the civilization of England, and of the most progressive European countries as well as that of the northern United States, and all other parts of the world that have been peopled by colonization from European stock, wherever the climate permits.

Another example of the failure of health of Europeans largely as the result of restricted diet improperly selected is found in Newfoundland and Laborador. In both these districts occurs the deficiency disease beriberi, which is caused by lack of a sufficient amount of the dietary essential water-soluble B. The disease is the same that is seen so frequently among the poor laboring classes of the Orient who subsist largely on a diet of polished rice and fish with a few vegetables. The diet in Newfoundland consists, according to Dr. Little, of bread made from bolted wheat flour, tea, fish and salt meats, and raisins. A similar food supply is all that is available in Laborador.

There seems to be good reason to believe that a second deficiency disease actually occurs among the people of both of these regions as the result of their restricted and faulty diet. I refer to a condition popularly called night blindness, which is common, especially among men who are out at sea for a considerable period and are subjected to a fare of poorer quality than that obtainable at home. I cannot affirm that it is demonstrated that this is incipient xerophthalmia due to a lack of the unknown dietary complex found most abundantly in butter fat and a few other fats, but there is good reason to believe that it is. Night blindness occurs among men in lumber camps in Canada and

elsewhere, and the popular local remedy is to feed the patient milk or cheese. Prompt recovery is said to follow this modification of the diet. In these camps the food supply is frequently limited for considerable periods to bread, salt or canned meats and peas or beans. This again is a seed and meat diet, and has been found to be unsatisfactory for animals and for man. The same condition appears occasionally to be encountered in Japan, and is not uncommon in parts of India. In both these countries the popular remedy is the free use of liver as a food, and in India it is recommended that a poultice of liver be applied to the eyes as well. It is safe to say that it is the consumption of the glandular tissue that results in benefit to the eyes of the sufferer. In Japan eel fat and chicken livers enjoy the reputation of being efficacious in the cure of xerophthalmia. Night blindness is reported to be encountered in Russia somewhat commonly during the latter part of the Lenten fast. During this period the people restrict their diet largely to cereals, and fail to secure enough of the dietary factor which is concerned with the deterioration of the eyes.

According to the views of those who believe that climate in itself is the chief factor in determining progressiveness, it will never be possible for people in central Asia to develop a high state of civilization. It seems worth while to examine into the validity of this conclusion, and in doing so we must make clear what conditions we accept as a fundamental basis of civilization. If physical well-being as exemplified in excellent development, together with courage and energy, be the first requisite, we have in the past and have now some notable examples of it among the tribes of central Asia. In order to reach a high degree of civilization, however, it is necessary that a relatively high stage of mental development, together with both social and political fixity, shall be attained.

Of fundamental importance for the development of a highly organized society and a state of advanced civilization is the right kind of religion, since this determines the mental attitude of the individual toward his associates, his neighbors and his own destiny.

The Mongol hordes of central Asia in the thirteenth to the sixteenth centuries overran and conquered much of western Asia and Europe as far westward as the boundary of Austria-Hungary. Eastward they overran a large part of China, and to the North they were for generations a thorn in the side of the Russians. These Mongols, who played so prominent a part in history, were typical representatives of the sour

milk drinkers so common among the pastoral peoples of parts of Asia and eastern Europe. At the present time the natives of northwest Mongolia have many cattle, sheep, horses and camels, and derive their sustenance almost entirely from their flocks and herds. The Mongols had all the elements necessary for the creation of a high development of civilization except the mental attitude toward society that would permit them to respect the personal and property right of others. They had not the sense of honor and the appreciation of the ethical relations between man and man that are necessary for the establishment of a stable society based on law and order, and governed in the interests of the people. Such governments had not at that time gained popularity anywhere in the world. The frame of mind that makes possible these things can be attained only through the establishment of the best systems of ethics and religion. Climate has nothing to do with these.

It is significant also that the Chinese, while possessing a civilization of great antiquity, have lacked certain qualities that are necessary for the formation of a great nation. For many centuries they were overrun by successive waves of invaders from the northwest. The Chinese have always lived on a diet derived from cereals, legume seeds, tubers, fleshy roots and meats, together with a liberal addition of green leafy vegetables and some eggs. The widespread practice of sprouting grains preliminary to their use as human foods is justified by the results of modern science. The consumption of a large amount of leafy foods has, I believe, been a factor of the greatest importance in promoting their well-being, for as has been already mentioned, the leaf of the plant possesses dietary properties very different from those of the seed or other storage organ. These special properties are those that are necessary to correct the deficiencies of the seed, tuber, root or muscle meat type of diet. It is perhaps significant in this connection that the Chinese have, on their diet in which the leaf was almost the sole protective food, been unable to cope with their sour milk drinking neighbors to the northwest. The descendants of these waves of invaders still live in China, forming classes that have never been assimilated socially.

The ancestors of the present Turks were likewise a pastoral people and were sour milk drinkers. This constituent of their diet alone would suffice to make it highly satisfactory, and to insure, in the absence of contagious or of insect-borne diseases, an excellent physical development. Such a development is the essential basis of military ambition and success, and was possessed by both the Mongols and the Turks.

Almost every one is familiar with the conclusions of the famous Russian bacteriologist Metchnikoff, that the remarkable number of centenarians among the Bulgarian peasantry is the result of the ingestion of sour milk. Metchnikoff believed that the remarkable results of the regular use of their simple diet was due to the lactic acid producing organism which causes the souring of the milk. He attributed its beneficial effects to the production of lactic acid by this organism in the intestine, and the inhibition of the growth of the harmful putrefactive organisms which develop there in the residues of protein rich foods. He attributed the early aging of mankind and of animals to the absorption of these toxic products.

It is of more than ordinary interest that the most modern investigations in the field of nutrition, carried out by methods that far surpass those of the past in scientific accuracy, support his observations in a general way as regards the beneficial effects of the diet of the people he observed, but detract from the importance of the organism that the milk contains. It is the correction of the deficiencies of the types of diet that consist mainly of seed products, tubers or fleshy roots and muscle meats, by the inclusion of the protective food milk, which greatly improves health and increases vigor. The bacteria in the milk are of secondary importance.

The Arab of today is an example of the effects of a diet in which sour milk finds a prominent place. He is described by all modern writers as singularly handsome, tall and lithe, with beautifully molded limbs. Dwarfs, hunchbacks and misshapen persons are seldom seen in Arabia. Few races of humanity excel the Arab either physically or morally. The Arab derives his sustenance in great measure from fruits and milk. Most of the milk is soured, but this forms the most prominent constituent of his diet. In fact, under the names sheneena, leben, yohourt, keffir, koumiss, matzoon and dadhi, soured milks have been used from earliest times very extensively over a large part of central Asia as well as Egypt, Palestine, Arabia, Turkey and the Balkan States. Wherever fermented milks are extensively used as food the physical development of the people is usually good, and the length of life exceptionally long in many instances.

Huntington believes that the climate of China makes impossible the development of a highly progressive race. This does not seem justified without taking into account other factors that are of importance in

this connection. We must agree on what conditions are essential to the development of a high state of civilization before we can agree on other points.

In a sparsely settled country, where the care of flocks and herds is the only means of livelihood, as is the case over large areas of Asia, pasturage and water are likely to be greatly prized, and the rights to them sharply contested. Enmity between neighbors, lack of education, and the consequent lack of opportunity to gain ideas from others through reading, lack of incentive to do anything other than seek the protection of the animals that contribute to the comfort of man, are themselves reason enough for the lack of development of a high state of civilization. The climate need not necessarily be responsible for the result. The energy and aggressiveness of people who have dwelt in such regions have been repeatedly exhibited in wars of conquest. They have the physical development and intelligence necessary to form the basis of a civilization, provided the necessary conditions for its growth are existent.

It is necessary, in order that a civilization may develop, that food, shelter, clothing, and other comforts of life shall be obtainable without too great a drain on the physical resources of man. There are several reasons why these conditions are best fulfilled in the cooler parts of the temperate zones where the rainfall is most satisfactory for the growth of farm crops.

One of these conditions is that the winter in these regions destroys certain insects that would otherwise destroy the crops. Certain disease transmitting organisms, such as the cattle tick and the tsetse-fly, which bear respectively the Texas fever and the sleeping sickness, do not survive the northern winters, and the population in these regions enjoy freedom from these diseases. Cold winters limit the number of species of weeds and other obnoxious plants, and render the production of useful crops less laborious. These are factors of the greatest importance to agriculture and to the well-being of man.

Wherever insect life, such as the destructive ants of tropical forests or myriads of mosquitoes and other insects, detract from the comfort of man, and where rank vegetation renders futile his efforts at clearing ground for cultivation, and where diseases destroy his domestic animals, and place in his own blood disease producing organisms that rob him of his vitality and ambition, man must have recourse to power other than his own strength to overcome obstacles. If we give him the aid of

machinery and control over suitable sources of power to free him from his crushing burdens, and the aid of science to free him from the scourge of disease, and a diet that causes him to develop a high state of physical perfection, we may confidently expect of him any development of mental traits consistent with his heredity. It is the aim of those who direct the great agencies for the promotion of hygiene and public health to bring to the inhabitant of the Tropics these blessings. They have faith that these inhospitable regions can ultimately be made the seats of creditable human society. Not until all of these problems have been solved, however, will man succeed in the less hospitable parts of the world.

One not infrequently sees in discussions of this nature the statement that in warm regions, where food is easily obtainable, and little shelter or clothing is necessary to the comfort of man, he sinks into indolence, and remains in a state of ignorance and degeneracy. It is urged that only in such a climate as necessitates exertion and foresight during the summer in order to provide food, shelter and clothing with which to pass a severe winter in comfort, will man develop in a satisfactory way the higher virtues of civilization. The theory has been postulated that energy, aggressiveness, frugality, foresight, inventiveness, solicitude for dependents, respect for property rights and the other virtues of man in his most highly advanced condition, are best fostered in a climate that offers vicissitudes, and requires that the life of the individual shall be a struggle with his environment.

Others tell us, and it appears logical, that so long as man is forced to spend his days in a struggle for existence he cannot develop his higher mental qualities. It is said that the creation of an aristocratic element in society, whose wants are supplied by the labor and sacrifice of a less fortunate group, establishes the ideal condition for fostering the mental growth that comes from reflection and the study of the ideas of others.

There is doubtless an element of truth in each of these views regarding the conditions under which man will best develop his mental capacities. Leisure is essential to certain types of creative thought. Thought is stimulated profoundly through discussion, reading and observations of the phenomena of nature. It is not yet demonstrated, however, that such creative thought is possible or probable only in temperate regions where there are frequent and pronounced changes in temperature.

Let us now return to the relation of the diet to physical efficiency. We have, I believe, a very important problem to solve in the education

of the public in many parts of the United States in the proper selection of food. There are large numbers of people who are living too largely on diets derived almost exclusively from wheat flour, cornmeal and polished rice—all of which represent the poorest parts of the kernels from which they are manufactured—together with oats, peas and beans; tubers such as the potato, and edible roots such as the sweet potato, beet and turnip, supplemented with muscle cuts of meat. This type of diet is not satisfactory for the nutrition of an omniverous animal unless it is supplemented with milk or the leafy vegetables in liberal amounts. Of somewhat lesser value as corrective foods are eggs and the glandular organs of animals. These are, however, very low in calcium and so fail to make good this important fault in the diet.

Early aging and low vitality with consequent susceptibility to disease attend the adherence to an unsatisfactory diet. This conclusion has been forced on my co-workers and myself as the result of thousands of observations on animals restricted to diets varying in quality and restricted as to source. Variety, palatability and appropriate chemical composition as revealed by the best methods of analysis at our disposal, do not necessarily guarantee safety. Chart 3 illustrates this fact.

The general public becomes suspicious when approached by a multiplicity of councilors seeking favorable consideration when the character of their advice is so bewildering. The trouble lies in the lack of definite and accurate knowledge concerning the chemistry of nutrition that has prevailed until very recent times. While many of the wisest philosophers would agree with the statement expressed editorially by the *British Medical Journal* in 1904, "The study of dietetics should be looked upon as very nearly if not quite as important as the study of therapeutics," much disagreement would, nevertheless, be encountered in their views as to the best dietary habits to adopt. Fortunately, chemistry has come to rescue dietetics from its state of empiricism. In the hands of the chemist new methods of experimentation have been developed that have made possible the solution of problems of detail not dreamed of in the philosophy of dieticians.

There is still some scepticism among thoughtful people as to the importance of diet in its relation to health and disease. This is the natural result of several factors. In the first place we accept as normal such conditions of nutrition as we are accustomed to, until it is demonstrated that a higher standard is easily attainable. We are accustomed

Explanation of Plate III

Chart 3.—It has been customary among some investigators in recent years to assume that a diet which is capable of inducing growth at a good rate for several weeks or months is to be regarded as satisfactory. My colleagues and I have, however, reached the conclusion that judgment can be safely formed only after the effects of the diet on the life history of the animal have been observed. This, there is every reason to believe, applies also to man.

This principle is illustrated by the curves of rats fed on different diets presented in chart 3. Lot 2,152 was fed cereal products, peas, beans, calcium carbonate, and sodium chlorid. One of the animals in the group grew fairly well for three months, then failed rapidly and died.

Lot 2,153 took the same diet supplemented with 10% of round steak, which we know improved the diet essentially only in respect to the quality and quantity of its proteins. This improvement caused an acceleration in the rate of growth and made possible a period of several months of apparent well-being after growth ceased. The full adult size was not attained, however, and the fraction of its life following the completion of growth and preceding decline was very short as compared with what it is possible to attain in well-nourished animals.

Lot 2,070 was fed the same diet as lot 2,153 but further improved by the inclusion of both whole milk and cabbage. When these additions were made growth was more rapid and extended over a longer period. The span of life was greatly prolonged, the most prominent feature being the extension of the period of full vigor in adult life.

From such facts as I have been able to collect concerning the nutrition of certain of the people of India, the Bahama Islands, the Philippines and a few other places, I am led to conclude that man in some parts of the world is attempting to live on diets of about the same quality as that described in connection with lot 2,153. It would be very instructive if our geographers would seek to eliminate diet as a possible factor which complicates their deductions concerning the importance of climate in determining the achievements of man.

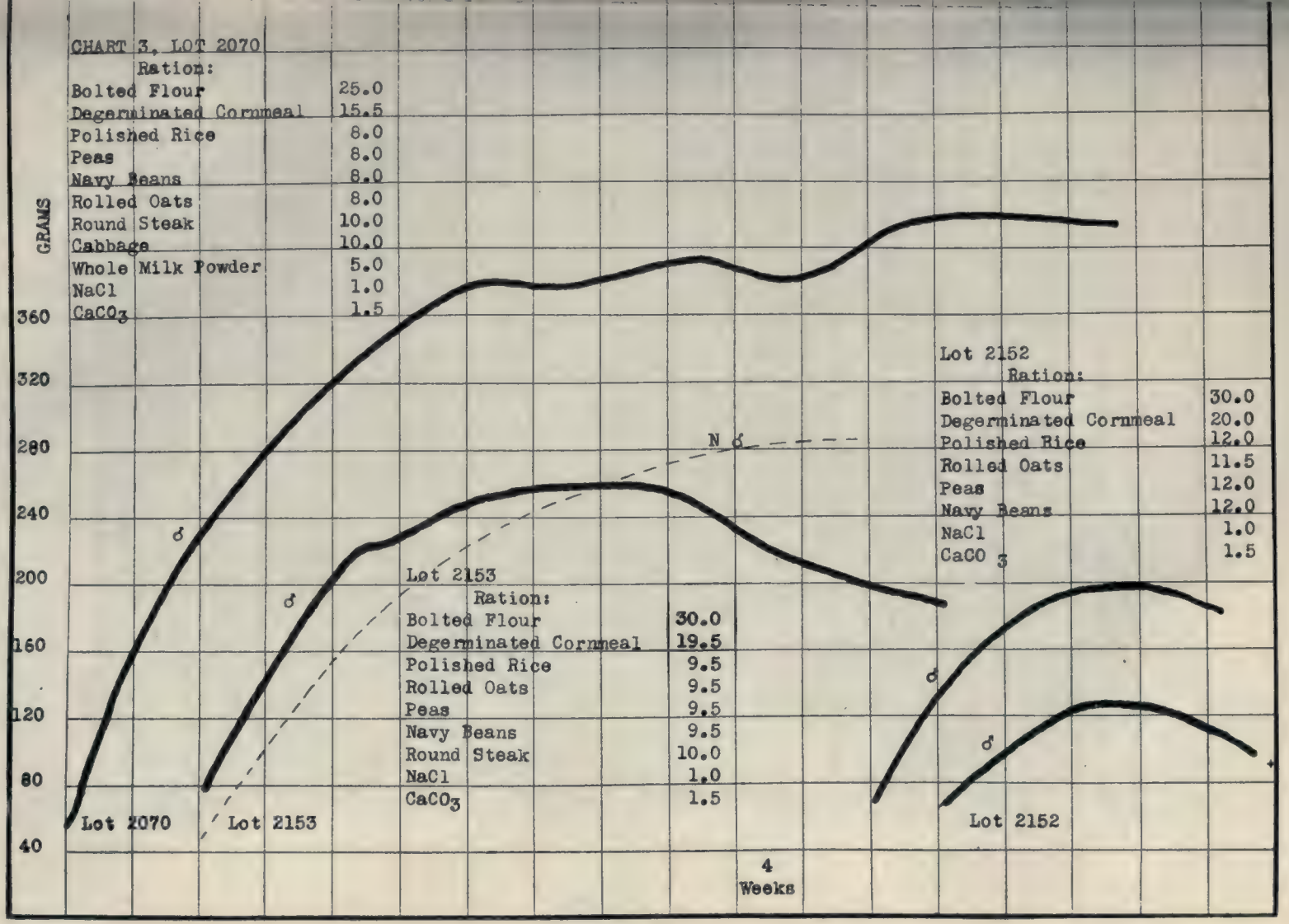
CHART 3. LOT 2070
Ration:
Bolted Flour 25.0
Degerminated Cornmeal 15.5
Polished Rice 8.0
Peas 8.0
Navy Beans 8.0
Rolled Oats 8.0
Round Steak 10.0
Cabbage 10.0
Whole Milk Powder 5.0
NaCl 1.0
CaCO3 1.5
GRAMS
360
320
280
240
200
160
120
80
40
♂
♂
N ♂
Lot 2070
Lot 2153
Lot 2153
Ration:
Bolted Flour 30.0
Degerminated Cornmeal 19.5
Polished Rice 9.5
Rolled Oats 9.5
Peas 9.5
Navy Beans 9.5
Round Steak 10.0
NaCl 1.0
CaCO3 1.5
Lot 2152
Ration:
Bolted Flour 30.0
Degerminated Cornmeal 20.0
Polished Rice 12.0
Rolled Oats 11.5
Peas 12.0
Navy Beans 12.0
NaCl 1.0
CaCO 3 1.5
♂
♂
Lot 2152
4
Weeks

PLATE III

to see people old looking at 30 to 40 years of age, and do not become impressed by it, even though the occasional preservation of vigor to an advanced age shows us what is possible.

The results of malnutrition are not such as to force themselves on the attention. It is attended by languor but not by pain. The effects of heredity and disease are not infrequently responsible for poor physical development which is scarcely distinguishable from that due to faulty nutrition. Man in different regions lives on diets that are widely different in character, and succeeds sufficiently well to seem to warrant the conclusion that it makes little difference what kind of food he takes, so long as it is wholesome and he has enough. The fallacy of such an assumption becomes apparent in the light of what we now know of the dietary properties of each of the more important natural foodstuffs. We can readily see now that man in different parts of the world is living on all the types of diet on which it has been found possible to nourish animals, and on no other. In certain places he is attempting to live on diets that cost him his vitality by the time he has reached the age which should find him enjoying the full vigor of middle life. This is the seed, tuber and meat type of diet which has already been described.

Throughout parts of India, China, Japan, the Philippines, eastern South America, Newfoundland and Labrador, beri-beri is common, and is due to faulty diet of a character which we well understand. Those who live almost exclusively on a diet of degerminated seed products, tubers, roots and muscle meats do not miss by a very wide margin developing this disease.

While scurvy has become a relatively rare disease among adults, it is still common among infants whose sole food is heated milk. We now know that the antiscorbutic substance, water-soluble C, is the most unstable complex in the diet, and is readily destroyed by heating to the boiling point of water. Many people who live almost exclusively on cooked foods come very near the point of specific starvation for this particular substance, and narrowly escape developing the disease.

Dr. Goldberger of the Public Health Service has done notable work in the study of the relation of the diet to pellagra in the South. He has pointed out that the diet of the pellagrin consists essentially of degerminated cereal grains, starch, sugar, molasses, sweet potatoes and fat pork; a very small amount of green leafy vegetables are eaten and practically no milk. He has improved the diets of the inmates of institutions where pellagra was a scourge, and observed that this leads to the

eradication of the disease. While living on a satisfactory diet, he and his associates were not able to contract the disease by material from the lesions from pellagrins and with their excreta. Further special studies, made in villages where pellagra was common, showed that families using liberal amounts of milk rarely contracted the disease, and that its incidence was highest in those households in which least milk and green vegetables were used. The liberal use of the articles that, as the result of animal experimentation, have been discovered to be corrective in character prevents the occurrence of pellagra. The question as to whether it is a disease due to an infectious agent has not been definitely decided.

It is significant that the incidence of tuberculosis among the general population of a city such as Baltimore is much higher among the group of people who live almost exclusively on the bread, meat and potato type of diet, and use least milk and green vegetables. If we may safely draw deductions from animal experimentation, it appears probable that this diet predisposes to infection with the tubercle organism.

Many will not agree with this conclusion, but hold that poor hygienic conditions and opportunity for infection, racial susceptibility and certain trades, are the factors that make this disease common. To this view I would reply that we know that the diabetic patient, whose vitality is lowered both by failure of one of the normal processes of metabolism —the oxidation of sugar—and by faulty diet, as is practically always the case, is extremely susceptible to tuberculosis. The medical profession has for many years recognized that one of the most valuable therapeutic agents in this disease is good nutrition. It is interesting to note that on purely empiric grounds the profession long ago came to the employment of a diet for the tuberculous which contained liberal amounts of milk and eggs.

Of special interest in connection with the problem of susceptibility to tuberculosis is the noncitizen Indian of today. No group of people anywhere is dying more rapidly from tuberculosis. The Indians live outdoors all summer, and probably have throughout the year as much fresh air as the average city dweller. They have abundant opportunity for becoming infected because of their careless association with infected persons, and reckless dissemination of infected sputum. Racial susceptibility has been generally regarded as a satisfactory explanation of the prevalence of tuberculosis among these Indians. It seems to me that there is another and more important factor involved, namely, the

unsatisfactory character of their food supply. The noncitizen Indian lives on a reservation and is supported by the government. He has, in general, no interest in agriculture, and does not raise much of his food. His live stock usually consists of horses. He lives on the products that he buys at the agency stores, and these, unfortunately, consist almost wholly of degerminated cereal products, legume seeds, tubers and meats. It seems plausible that this diet is an important factor in rendering him susceptible to this rather mildly virulent infection.

In the light of modern nutrition studies we have come to regard as unsatisfactory some of the diets widely used by man. We have demonstrated that, in certain respects, there is a close parallelism between the history of a poorly nourished animal and a poorly nourished man. Much remains to be learned of the finer details of the dietary habits of man in various parts of the world, and of the health conditions with which these can possibly be correlated. It has seemed, however, that we have succeeded in correlating certain data relating to human nutrition with the results of laboratory studies in a manner which brings to light a most important principle in the selection of foods. If these deductions are sound, it is evident that one of the great tasks of the general undertaking of raising the standard of public health is the education of the public along two lines: the extension of the use of dairy products, and the cultivation of the habit of eating more freely of green leafy vegetables than is now the practice in the United States.

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REMARKS ON THE CHEMISTRY OF THE PROTEIN MOLECULE IN RELATION TO INFECTION

ABSTRACT

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About twenty-five years ago I decided to give the greater part of my time to study of the chemistry of bacterial cells. The first thing to do was to get the cell substance in large amounts, relatively free from contamination. Up to that time, bacteria had been grown in test-tubes and Roux flasks, the latter containing the largest cultures made. I tried Roux flasks. I inoculated 100 of these flasks. The bacteria grew abundantly, but when I attempted to detach the growth and fish it out of the relatively small neck of the bottle it was so difficult that I had to give it up. Next I tried to grow bacteria in moist chambers, but found that, using every precaution, they invariably became contaminated; and finally, in 1900, I devised copper tanks for growing bacteria in massive cultures. Some of you have seen these tanks and others have seen the illustrations. By means of these tanks I was able to obtain bacterial cell substance in large amounts — literally by the pound, of pure cell substance. It cost at that time $75 to load my nest of six tanks, each tank being 10 feet long and 2 feet wide, so that with the six I grew 120 square feet of germ substance at a time. I imitated the scientific farmer and rotated my crops. As a routine, I inoculated my tanks with pneumococcus and grew this organism at from 38 to 40 C. for 4 days; then I removed the growth, resterilized my medium, and planted typhoid bacilli. I found that typhoid bacilli grew just as well after pneumococci as on perfectly fresh material. After the growth of typhoid bacilli had been removed, I resterilized and planted the colon bacillus. Usually I got two good crops of this organism. After removing the second crop of colon bacilli I grew other crops of non-pathogenic bacteria. A good yield from the 6 tanks often gave me as much as 500 gm. of pure bacterial cell substance. The growths were detached with sterilized bent glass rods and pulled into sterilized receptables by means of a water pump. The bacterial substance was washed first with salt solution and then extracted for 3 days with

absolute alcohol and for 4 days with ether. In all cases this treatment left a white powder, all the coloring matter having been removed by the extractions.

The extracted cell substance was ground first in porcelain and then in agate mortars. The only accident of any note happened while grinding the bacilli. We found it necessary to wear masks, and even when this was done and typhoid bacilli were being ground, the one who did this for the first time had within from 4-6 hours a severe chill followed by a temperature which ran as high as 106 F. After the subsidence of this fever there was no further trouble. I found that this cellular substance under the microscope showed the bacilli as normally as they appear in fresh specimens. The pneumococcus, for instance, appeared quite as normal after this treatment as it does in a specimen of sputum. I found that this dead cellular substance, injected into animals, did them harm, and I found — strange to say — that it harmed in inverse proportion to the infectivity of the living organism. Note that the prodigiosus, a nonpathogenic organism, killed guinea-pigs when injected into the abdominal cavity, one part to two or three million parts of body weight, while the anthrax bacillus required one part of cellular substance to 1,400 parts of body weight. In no amount did the tubercle bacillus kill fresh animals. The more infectious an organism is, so far as those with which I worked are concerned, the less toxic I found it when injected into animals. Understand that I am saying nothing about toxins or antitoxins or toxin immunity. I am talking about micro-organisms that produce no extracellular toxins. The word "toxin" has come to have a definite meaning. It is a substance which, when injected in repeated nonfatal doses, causes animals to produce an antitoxin. I do not refer to diphtheria or tetanus, or any of the bacteria which produce soluble toxins. So far as the endotoxin of Pfeiffer is concerned, I have never found such a thing. In other words, I have never found in any cell substance a substance which, when injected into animals, produces an antitoxin. The protein poison is not a toxin. I found that the dead substance, injected into animals, produces the same lesions that follow inoculation with the living bacillus. When I inoculated an animal with the typhoid bacillus or the colon bacillus intra-abdominally I got the same symptoms and the same lesions as when I injected living typhoid or colon bacilli. I concluded that it is not the growth and multiplication of bacteria in the animal body that causes the symptoms and lesions of the disease.

When I was a student I was taught that the characteristic lesions which we find in the intestine in typhoid fever result from the gnawing action of typhoid bacilli in their attempts to get through the intestinal wall into the blood. Indeed, for some years I taught the same thing. Today we admit that this is not the case, and that typhoid bacilli in passing from the alimentary canal into the blood produce no recognizable lesions and that the lesions which we find in the majority of cases — not in all — after death from typhoid fever are due to the elimination of poisonous substances from the blood and do not indicate the port of entry of the bacteria. I wish to say, parenthetically, that many years ago I tried to induce ulceration in the stomach and intestine by feeding animals with arsenic. I did not succeed, but I found that it was relatively easy to induce these ulcerations by giving a preparation of arsenic hypodermically or intravenously. Moreover, on looking up the literature I found that this method of producing gastric and intestinal ulceration was known one hundred and fifty years before I made my experiments.

As I have said, the effects after the administration of dead bacterial cell substance are the same or at least very similar to those which follow inoculation with the living organism, and that the effects of the dead substance are inversely proportional to the infectivity of the living organism. Why is it that the prodigiosus is nonpathogenic to guinea-pigs? I should say it is because the normal secretions of the body cells destroy these bacilli as soon as they get into the blood. In other words, the body cells are already sensitized to this organism. Therefore it follows that if you take enough of the dead cellular substance of the prodigiosus and inject it into the abdominal cavity of a guinea-pig, immediately the normal fluids of the body split up the cells of the prodigiosus, and if the quantity be sufficient it kills the animal. In my opinion the infectivity of a bacillus or other virus depends on two conditions:

1. Will it grow in the animal body? If it will not grow in the animal body it cannot cause infection. A given organism must grow and multiply in the body in order to be infectious, and in doing so it must be able to feed on the substances of the body. If it is not able to do this, it cannot be infectious to that animal.

2. Whether a given organism is pathogenic to a given animal or not will depend on whether the fluids of the body kill that organism as

soon as it is introduced into the body. If this does not happen, and if these two conditions are favorable, the micro-organism grows and multiplies in the body and causes infection.

I attempt to explain vaccination in this way. The smallpox virus is pathogenic to the person who has not had smallpox, or to the man who has not been vaccinated. To the person who has had smallpox or who has been successfully vaccinated the smallpox virus is not pathogenic. When you vaccinate a child against smallpox you introduce into the body a modified smallpox virus. It grows slowly and the body cells are educated and trained to destroy this virus. When subsequently the child is exposed to smallpox the first smallpox virus that gets into the body is split up and destroyed, and there is no growth and no disease.

We vaccinate against typhoid fever by taking the dead bacillus and injecting it into the individual three or four times at intervals. In so doing we are training the body cells to digest the typhoid protein and subsequently when the man drinks water that contains typhoid bacilli, as soon as the first organisms get into the body they are split up and destroyed, and the man escapes typhoid fever.

Twenty years ago I made the statement that typhoid and like vaccinations will not give absolute protection. Such protection is always relative and may be overcome by massive inoculations. From experience in the late war we know that massive doses of typhoid bacilli may cause typhoid fever in the vaccinated. Furthermore, we have learned that typhoid fever in the vaccinated differs neither in symptomatology nor in lesions from that in the unvaccinated. An unwarranted faith in the value of vaccination against typhoid fever gave some of our medical officers in France a feeling that this disease could not occur among our troops. It happened, therefore, that in at least one instance typhoid fever was first recognized at necropsy.

If we inject into the abdominal cavity of a guinea-pig a virulent culture of the colon bacillus and then observe the symptoms, we shall find them to be about as follows:

For some hours there is no recognizable difference between the inoculated animal and his fellows. Their behavior is the same. Then, rather suddenly, something goes wrong with the inoculated animal. It begins to shiver, its coat gets rough; it huddles up among its fellows; it goes off its food; something is wrong. For a while its temperature may be above the normal, but in a short time it begins to fall and con-

tinues to do so until the animal dies. At necropsy one finds an exudative hemorrhagic peritonitis. If something like the minimum fatal dose has been administered, it will be about twelve hours before the animal shows any changes. This is the period of incubation, and it occurs in every infectious disease. During this time, the bacilli rapidly multiply in the body. They are feeding on body substances. They are converting guinea-pig substance into typhoid substance, and the process is a synthetic one. They are taking relatively simple bodies, probably only amino acids, and building them into typhoid protein. During the period of incubation of an infectious disease the invading organism furnishes the ferments and the body of the host supplies the substrate or food, and the processes are synthetical. Simple bodies are built into more complex ones. There is no poison set free, there are no lesions, and there are no symptoms. Therefore it is not directly the growth and multiplication of bacteria in the body that cause the symptoms and lesions of the infectious diseases.

Really the period of incubation is a critical time, as it always to some extent at least determines how rapidly the bacteria grow. The invading organisms multiply in the body until the body cells become sensitized and pour out a secretion that splits up and destroys the invading organisms. During the active stage of an infectious disease the body cells supply the ferment, the invading organisms furnish the substrate or food; the processes are analytic; complex bodies are split into simple ones; a poison is set free, and the symptoms and lesions of the disease develop. I do not desire to give the impression that I believe there is a sharp line between the processes of incubation and those of the active disease. The two may be going on side by side in adjacent tissue. The sensitization may be local or general. In the former instance, a local disease develops; in the latter, the disease is systemic. The sensitization may come on suddenly and with virulence; it is then an acute disease. It may come on slowly and gradually extend, and it is then a chronic disease. It is the destruction of the bacilli in the body that causes the symptoms and lesions of the disease.

To a second guinea-pig we give in place of a living culture the dead cellular substance of the colon bacillus. This organism has been grown in vitro. There is no chance for multiplication in the body. The period of incubation is now shortened. Dead cellular substance, having no resistance, sensitizes the body cells more quickly than living bacilli. After sensitization occurs we have exactly the same symptoms that

we had in the animal that we had inoculated with the living culture. On postmortem examination we find the same exudative hemorrhagic peritonitis.

My assistants and I worked for some years in our endeavors to find methods for splitting bacterial cell substance into poisonous and nonpoisonous parts. The method which we finally adopted was to boil the cellular substance at 78 C. in absolute alcohol in which 2% of sodium hydroxid had been dissolved. An aqueous solution of the same alkali will produce the same result, but in this case both the poisonous and nonpoisonous parts will be in solution. When absolute alcohol is used the poisonous part is soluble in the alcohol, while the nonpoisonous part is not.

Having found that pathogenic bacterial cell substance could be split into poisonous and nonpoisonous portions it was quite natural that we should attempt to find out whether nonpathogenic bacterial cell substance could be split in the same way. I have already indicated that we found this to be true. Next we tried animal and finally vegetable proteins. To be brief, we came to the conclusion that all protein molecules contain a poisonous portion. As I have indicated, this is a poison, and not a toxin. In its gross effects on animals this poison is the same, whatever the protein from which it has been derived. I dare say that it will be found on closer study that there are differences in chemical composition and structure, between the protein poisons obtained from widely different proteins. It is interesting to remark that so simple a protein as casein will furnish enough protein poison to kill guinea-pigs when it is injected intravenously. I am sorry that I have not shown myself to be a sufficiently skilled chemist to work out the chemical structure of the protein poison. I must leave this for more competent men. The dose of the poison necessary to kill a guinea-pig when injected intravenously is about 0.5 mg.

We have made many attempts to induce immunity in animals with the protein poison. We have found, and others have confirmed this, that a certain degree of tolerance may be established by repeated doses of this substance. This tolerance is not marked. I do not think that it should be called a form of immunity. Still I am inclined to believe that it has an important part, under certain conditions, in securing immunity. If guinea-pigs or rabbits that have been treated with successive doses of the protein poison, and so trained that they will stand without harm two or three times the ordinary fatal dose, be inoculated

with a living organism, it requires more of the culture to kill these animals than it does to kill fresh animals. In other words, increased tolerance to the protein poison enables an animal to bear at least one fatal dose of the living organism. When it recovers from the living organism it has acquired a specific immunity. In this way I have attempted to explain the often observed and frequently recorded fact that the seasoned soldier withstands epidemics to which the raw soldier succumbs.

In our observations on the fatality of the acute respiratory diseases in our armies during the war two facts stood out prominently. It was at first observed that the soldiers from rural districts succumbed in larger numbers to these diseases than those from densely crowded cities. The other fact equally striking was that when an epidemic struck a camp the recently recruited men died in larger numbers than those who had been in the camp for months. In the fall of 1917-18 it was observed that men recruited from rural communities showed a much higher death rate from the respiratory diseases than those from densely populated cities. When influenza struck the camps in the fall of 1918 recently recruited men died in larger numbers than did those who had been in camp for months. I have attempted to explain these observations on the ground that men from large cities and men who had been in camps for many months have acquired an increased tolerance to the protein poison. When measles or influenza came they were not immune to these new infections, but they bore them better, and in doing so, acquired a specific immunity. In one camp one-tenth of the command had been in camp less than one month when influenza appeared. This one-tenth furnished 30% of the deaths. Similar observations have been made in all wars, and in other armies during this war.

THE RELATIONS OF PROTEINOGENOUS AMINES TO MEDICINE

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INTRODUCTION

The injurious action which pathogenic micro-organisms exert on the human organism is almost entirely effected by chemical means. Yet our comprehension of the chemical processes by which bacteria produce disease and our knowledge of the chemical constitution of the poisonous substances evolved by their metabolism is in a very elementary state. To the student who would venture to dedicate his life-work to the investigation of the chemical factors in the pathogenesis of infectious diseases, the history of the last thirty years of the Nineteenth Century tells a tale that merits his reflection.

About the time when Pasteur, in France, had communicated his fundamental researches on fermentation and putrefaction, proving that these two processes depended invariably on the presence and activity of living micro-organisms, another chemist, in Italy, Selmi, was occupied in investigating the end-products of putrefaction found in human bodies after death. Selmi observed that basic compounds occcurred in the animal organism of similar chemical character as the alkaloids of vegetable origin, giving reactions like those of coniin, nicotin, atropin, delphinin and strychnin. Since he found these putrefactive alkaloids chiefly at the medicolegal examination of corpses, he gave them the name ptomaines, from πτῶμα — corpse. Selmi worked entirely with the extracts of the putrefied material and recognized the proper solvents in ether, chloroform and amylalcohol, but he himself never succeeded in isolating a single ptomaine in pure crystalline form. This achievement was accomplished by Nencki, one of the most eminent investigators in the field of chemical bacteriology. Nencki, in 1876, first isolated and analyzed correctly a base of the formula $C_8H_{11}N$ obtained in the putrefaction of gelatin and identified it later as phenylethylamin. Of the large number of investigators that followed Selmi and advanced this field, Gautier, in France, and Brieger, in Germany, were the most successful. By using new precipitating agents like the chlorids of the heavy metals, as mercuric and platinic chlorid, they

isolated many ptomaines of definite chemical composition and investigated their chemical, as well as their physiologic, properties. From organs, meat and foodstuffs, which had undergone putrefactive changes, Brieger isolated mono-amines (mono, di- and, trimethylamine, ethyl, amyl, and butylamine), diamines (putrescin and cadaverin) as well as cholin, muscarine and methylguanidine. In addition to these, he isolated a large number of compounds, so complicated that only their elementary composition could be determined. It became more and more apparent, especially under the influence of the work of Nencki and his school, that all these basic substances were formed as the result of the action of bacteria, on protein and phosphatids. By the early 80's it had been definitely proved that micro-organisms could cause disease, and adherents as well as opponents of the germ theory, constantly raised the question: How do germs produce disease? Brieger, with his followers, applied his methods to the culture mediums in which the bacteria grew, and succeeded in isolating from these a variety of ptomaines. Brieger himself isolated four different ptomaines from the culture filtrate of the tetanus bacillus, and later on, a typhotoxin from the typhoid bacillus, Rosenbach and Nicolaier described a tetanin, and in this way it was believed by many that bacteria caused infectious disease by virtue of these products of decomposition of the material on which they grew. This was soon proved to be a fallacy, for it was impossible with ptomaines alone to produce the characteristic symptoms of disease or the distinctive pathologic changes, whereas both could readily be produced by the injection of the culture fluid containing the bacteria. Ptomains produced by virulent organisms proved to be slightly toxic, whereas some nonpathogenic bacteria would form extremely poisonous substances. The ptomaines were found not to be specific for any one special micro-organism, nor could antibodies be produced in response to their injection into animals.

Not the study of the ptomaines, but researches on the true toxins and endotoxins, those soluble and intracellular poisons manufactured by the bacterial cell, brought about the new era in medical therapy. Antitoxin immunity and vaccination with attenuated cultures and virus accomplished results that heretofore were unknown in the history of medicine. It mattered little that the chemistry of these toxins and antitoxins was, and remained, unknown. Never before were short cuts in science more justified by the results. By new methods, not

chemical, Pasteur, the chemist, had opened this new continent, and with him Koch, Roux, Behring, Kitasato and Ehrlich plowed the fields on the fruits of which all medical men of today are living.

Thus it came about that just those bacterial poisons that chemically were the best characterized and studied, the ptomaines, were proved to be of little value in explaining the phenomena of infection and immunity, and in fighting disease. Although it is admitted that certain cases of food poisoning may be brought about by the action of ptomaines formed from the food by bacterial decomposition, most of these instances are proved to be the result of bacterial infection with the bacillus enteritidis or paratyphosus, or of bacterial toxin action, as in the case of the bacillus botulinus. The educated physician of today shrinks from using the word ptomaine, too often a misnomer for diagnostic ignorance and always tainted with the bad odor of its history.

This premature application to human pathology of the new facts gained from the study of the chemical substances formed during putrefaction proved to be an error, but the facts were correct and the knowledge of the process of putrefaction had been materially advanced. From this time the study of the putrefactive bases as being the result of the action of bacteria on protein and phosphatids, became more and more closely allied with the chemistry of proteins and of their building stones, the amino acids.

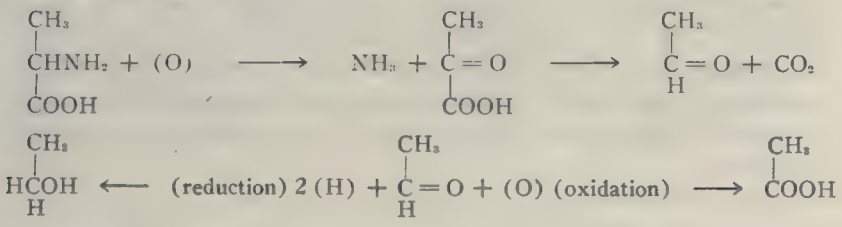
RELATION OF THE AMINES TO PROTEIN

When protein is disintegrated in the intestinal tract by the digestive activity of trypsin and erepsin, the result is the liberation of substances of simple structure, which are known as amino acids. These units are likewise obtained if the cleavage of the protein is brought about in the absence of the secretory enzymes of the digestive organs by the fermentative activity of micro-organisms, and this bacterial decomposition of protein matter to amino acids represents the first stage in the process of putrefaction. There are known at present some twenty different amino acids; they are absorbed — in part at least — intact from the intestinal lumen into the circulation and serve as food in the rebuilding of the tissue of every organ. All of them seem to be physiologically inert and, if introduced directly into the circulation, have no immediate pharmacodynamic action.

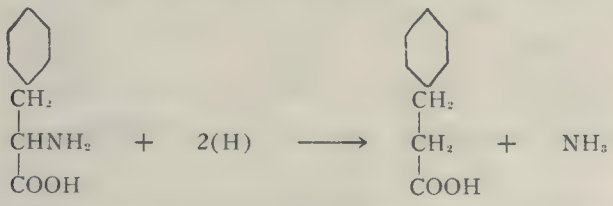
The decomposition of protein by bacteria or by organ cells does not stop when the amino acid stage has been reached. Bacteria have the

faculty of breaking the amino acids into smaller pieces, and some of these fragments are extremely toxic. There are two main routes over which this katabolism of amino acids may proceed.

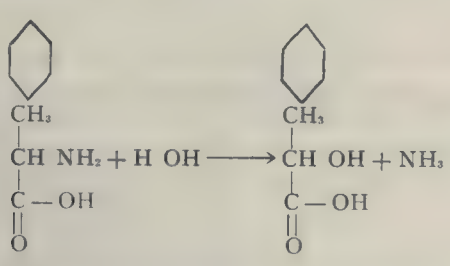
First: The amino group is detached, ammonia is split off and the next lower fatty acid is formed from the amino acid over the keto acid and aldehyd. This process is commonly accomplished by oxydation and is known as oxidative deamination. Thus alanine may be converted into acetic acid:



Anaerobic bacteria frequently reduce amino acids; ammonia is liberated and a saturated fatty acid formed. Thus phenylpropionic acid is formed from phenylalanine by this reductive deamination.



In rarer instances the oxyacid is formed from the amino acid by hydrolytic deamination.



By the activity of yeasts, on the other hand, alcohols are formed from the amino acids by hydrolytic deamination.

$$CH_3\ CH\ NH_2\ COOH + H_2O \longrightarrow CH_3\ CH_2OH + NH_3 + CO_2$$

Deamination is often followed by decomposition of the carboxylic acid formed, and by oxidation and demethylation. By this series of reactions paracresol and phenol are formed from tyrosin, skatol and indol from tryptophan. These are the compounds we are in the habit of thinking of when we hear the word putrefaction.

The second main route by which the breakdown of amino acids may proceed is the one to which I particularly wish to direct your attention. The carboxyl group is removed from the amino acid group by the splitting off of carbon dioxid. This process is known as decarboxylation. It may happen before or after deamination. If it precedes the splitting off of NH_3, basic substances, amines, of remarkable physiologic properties, are formed, and we define accordingly as proteinogenous those amins that are derived from amino acids by decarboxylation.

In this manner:

$CH_2NH_2—COOH \rightarrow CH_3NH_2 + CO_2$

$CH_3—CHNH_2—COOH \rightarrow CH_3—CH_2NH_2 + CO_2$

$(CH_3)_2CH—CHNH_2—COOH \rightarrow (CH_3)_2CH—CH_2NH_2 + CO_2$

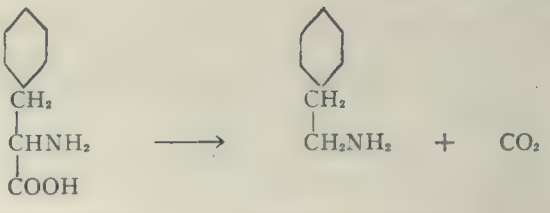
$(CH_3)_2CH—CH_2—CHNH_2—COOH \rightarrow (CH_3)_2CH—CH_2—CH_2NH_2 + CO_2$

$H_2NCH_2—CH_2—CH_2—CHNH_2—COOH \rightarrow H_2NCH_2—CH_2—CH_2—CH_2NH_2 + CO_2$

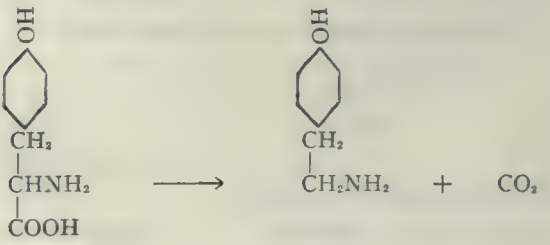
Ornithine — Putrescine

$H_2NCH_2—(CH_2)_3CHNH_2—COOH \rightarrow H_2NCH_2—(CH_2)_3CH_2NH_2 + CO_2$

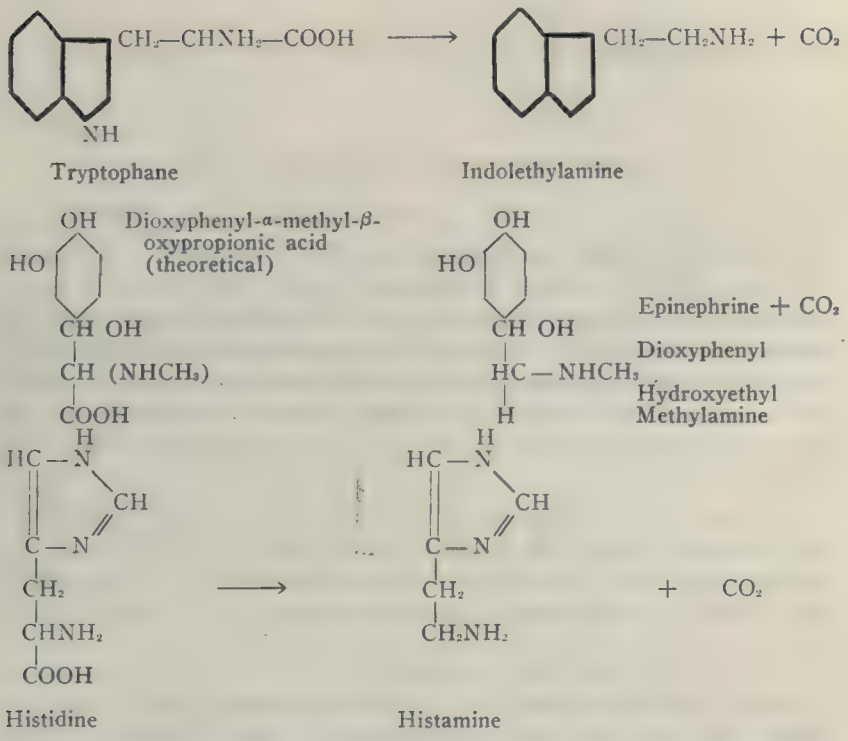
Lysine — Cadaverine



Phenylalanine — Phenylethylamine



Tyrosine — Tyramine



The removal of the CO_2 might be accomplished in various ways.

1. Directly

$$NH_2CH_2 - + C\ddagger = O \longrightarrow NH_2CH_3 + CO_2$$

2. By dissociation into the methylene derivative and formic acid and subsequent reduction of the first to the amine.

$$H_2N-CH_2-COOH \longrightarrow CH_2=NH + HCOOH$$

$$HCOOH \longrightarrow CO_2 + 2(H)$$

$$CH_2=NH + 2(H) \longrightarrow CH_3-NH_2$$

and

3. By hydrolysis.

$$H_2NCH_2—COOH + H—OH \longrightarrow H_2NCH_3 + HO—COOH \downarrow CO_2 + H_2O$$

which is similar to the hydrolysis of trichloracetic acid

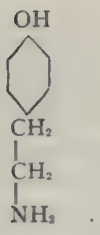
$$Cl_3C—COOH + H—OH \longrightarrow Cl_3CH + HO—COOH$$

This seemingly simple chemical process, the decarboxylation of amino acids to exceedingly potent substances of amine structure is of great theoretical, as well as practical, interest. The relation of this problem to the general nutrition of bacteria, to the metabolism of amino acids in the mammalian organism, to the pathology and pharmacology of the smooth muscle fiber system and to the chemical constitution of the glands of internal secretion, stamps it as a fundamental inquiry of biology.

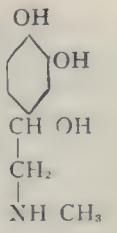
The systematic investigation of certain phases of these problems has been under way in the Sprague Institute for Medical Research for several years. But, before referring to our own work, I wish to discuss briefly the truly remarkable physiologic action of these amines.

PHYSIOLOGIC AND PHARMACODYNAMIC ACTION

From the point of view of chemical composition they might be divided into two classes: the mono amines, like isobutylamine, isoamylamin phenylethylamine, p. hydroxyphenylethylamine and indolethylamine, which have one basic N group; and the diamines, as tetramethylene diamine and pentamethylene diamin (putrescin and cadaverin) agmatine, the amine derived from arginine, and imidazolethylamine, which have two basic N groups. This difference in the chemical composition of each group is associated with a corresponding diversity of physiologic action. The most active compounds are those that have a ring structure with a side chain of two carbon atoms. As representative of the monoamines, p. hydroxyphenylethylamine will serve for our discussion. P. hydroxyphenylethylamine is derived from tyrosine by loss of carbon dioxide and is therefore also called tyramine. When injected intravenously in quantities of 1-2 milligrams into cats, dogs and rabbits it causes a sudden marked rise in blood pressure. This rise in blood pressure is pronounced and inferior only to the one produced by epinephrine, to which tyramine bears a striking similarity both pharmacologically and structurally.



Tyramine



Epinephrine

While the rise in blood pressure of p. hydroxyphenylethylamine is lower and slower than that of epinephrine, its duration is somewhat longer. Dale showed that the rise of the arterial pressure is partly due to an increased output of the heart, chiefly, however, to a vaso constrictor effect on the arterioles, peripheral in origin. In its action on the uterus, tyramine too resembles adrenaline; it inhibits the activity of the nonpregnant uterus causing relaxation of tonus in the cat, but produces intense contractions of the pregnant uterus. Thus the action on the animal organism produces symptoms which are similar to those produced by stimulation of the sympathetic nervous system. Especially marked is this action on the involuntary musculature of the eye. The intravenous injection of p. hydroxyphenylethlamine in the cat produces dilatation of the pupil, retraction of the nictitating membrane, widening of the palpebral fissure (lagophthalmus), protrusion of the eyeball (exophthalmos), and secretion of tears. Even after extirpation of the superior cervical ganglion these effects are still produced and they must therefore be considered peripheral in origin like similar effects of adrenaline. Of effects on gland cells, beside the lacrimal secretion, we might mention further the action on the sweat glands and submaxillary glands, sweat and saliva being secreted profusely. The flow of urine from the ureters is distinctly increased, but the pancreatic secretion is not visibly influenced and no glycosuria is produced even if as much as 100 mg. are given hypodermically. Nor does parahydroxyphenylethylamine show the dilatating effect on the smooth muscle fiber system of the bronchi, so characteristic of the action of epinephrine. Another important difference in the action of the two bases is shown in their mode of absorption by the organism. The action of epinephrine is almost entirely lost if given by mouth, while the tyramine retains its activity by this channel of absorption, producing all the symptoms of stimulation of the sympathetic nervous system in a marked degree.

The action of p. hydroxyphenylethylamine on the circulation in man is comparable to that in animals. If injected subcutaneously in doses from 0.02 to 0.06, it causes considerable elevation of blood pressure lasting for several hours. The increased systolic pressure is associated with a heightened pulse pressure and an increase of the volume pulse in the arm; the heart rate is retarded. In the electrocardiogram the ventricular complex shows an increase in the size of the T wave and the occasional occurrence of extra systoles (Hewlett).

The physiologic activity of parahydroxphenylethylamine was first revealed by Barger and Walpole, who recognized it as the chief pressure principle in extracts of putrid meat along with isoamylamine and phenylethylamine, which have a similar though lesser action.* On inoculating a culture medium of tyrosin with a small amount of human feces, Barger and Walpole were able to extract a substance which in the animal experiment behaved like parahydroxyphenylethylamine. This result induced them to express the probability that the amines isolated from putrid meat (parahydroxyphenylethylamine, phenylethylamine, and isoamylamine) are normally formed by putrefaction in the human intestine. Preceding this work of Barger and Walpole on the pressure principles of putrid meat, Dixon and Taylor had made the interesting observation that alcoholic extracts of the human placenta contained substances which on intravenous injection produced a rise of blood pressure and contraction of the pregnant uterus. But it was soon shown by Rosenheim that this effect was given only when the placentae had undergone putrefactive changes, as evidenced by the presence of micro-organisms. Dixon and Taylor had used an amount of alcohol, which, when mixed with the water content of the placenta, was insufficient to prevent putrefactive processes. When perfectly fresh placentae with sufficient absolute alcohol were used, no blood pressure raising substances could be extracted. The active substances were later identified as parahydroxyphenylethylamine and isoamylamine.

When parahydroxyphenylethylamine is given either by intravenous injection or by mouth for a long period of time, the effects of this slow, chronic poisoning are remarkable. Harvey fed and injected rabbits with gradually increasing doses of a 2 per cent. solution of tyramine,

* The discovery that extracts of putrefied meat raise arterial blood pressure on intravenous injection is usually ascribed to Abelous, who reported on this subject in 1906. But 50 years earlier P. L. Panum had discovered and described this fact showing that the poisonous substance retained its activity after boiling for 11 hours and after treatment with absolute alcohol.

over a period varying from 80 to 300 days. At the postmortem examination he found that 20 out of 33 animals showed renal lesions; in 25 there were lesions of the tunica media of the arteries; in 10 animals the enlarged heart showed fibrous changes. The daily subcutaneous injection of 3 mg. of parahydroxyphenylethylamine over a period of 2 weeks produces a severe anemia which leads to the death of the animal. The morphologic changes in the blood, as well as in the bone marrow, recall vividly the picture of true pernicious anemia in man (Iwao).

It might be mentioned that besides putrefied meat, other protein-containing material in a state of slow decomposition has been shown to contain the substance under discussion, such as several varieties of cheese: Cheddar and Swiss, and Japanese soja beans.

Another source of parahydroxyphenylethlamine which deserves our attention from different points of view, is ergot. Until about 10 years ago the action of this drug on uterus and blood vessels was ascribed to the presence of several alkaloids, such as ergotoxine, ergotinine, sphacelotoxin, cornutine and others. But as the result of the work of Rielander, Ackerman and Kutscher on the continent, and Barger and Dale in England, it was found that watery ergot extract contained parahydroxyphenylethylamine, isoamylamine, phenylethylamine, B imidazolethylamine, penta- and tetramethylenediamine and agmatine, and that the action of ergot on the uterus and blood vessels could be explained on the basis of the combined pharmacodynamic effect of these amines. It is still an open question whether these bases are produced entirely by the enzymes of the fungus itself, or by bacterial action during the not sterile process of extraction. In either case the notorious variability of the official liquid extract is readily intelligible.

This brings us to the second group of the simple amines derived from proteins: the diamines, which contain two nitrogen groups. To this group belong indolethylamine, the amine derived from tryptophane by loss of CO_2, putrescine and cadaverine, agmatine, the amine derived from arginine, and imidazolethylamine or histamine, the base derived from the amino acid histidine. The amine derived from tryptophane indolethylamine regarding its physiologic activity takes an intermediate position between the sympathomimetic monamines as represented by epinephrin or parahydroxyphenylethylamine and the diamines such as imidazolethylamine. The chemical structure shows a beautiful correlation to this physiologic action, for while the molecule of indolethylamine has two nitrogen atoms, only one of these is basic in nature.

We stated that the most active of these compounds are the cyclic amines with a side chain of two carbon atoms. Of the diamines it is the amine derived from histidine (α amino B imidazolepropionic acid) which shows such a structure. Its chemical name is B imidazolethylamine, but it may be appropriately called by its shorter name histamine. The physiologic behavior of this amine is primarily characterized by its stimulating effect on the smooth muscle fiber system.

If a guinea-pig weighing 300 to 500 gm. receives an intravenous injection of 0.5-1.0 mg. of histamine, the animal shows, a few seconds after the injection, a state of restlessness and exaltation. This is sometimes preceded by violent scratching of the ears, nose, and the skin of the body which can be reached by the paws of the posterior extremities. The guinea-pig, after a few turning movements, sits in a sprawling position; the heart beat is accelerated, and the respiration, first rapid, soon becomes irregular and labored. The animal passes urine and often feces. Suddenly it begins to run as though fleeing from an invisible enemy, then stops, and after several ineffective respiratory efforts, it falls to one side; the visible mucous membranes of the nose and of the genital region show a high degree of cyanosis. After a few veritable respiratory convulsions the animal dies, plainly a death from acute suffocation. At postmortem the lungs are found to be completely and permanently distended by air, they do not collapse, and are of a pale, anemic appearance, and sections show the bronchioles completely obturated as a result of a tetanic constriction of the smooth muscle fibers surrounding them. Atropine possesses a protective action against this death from acute emphysema and bronchospasm. When larger doses of histamine (3 mg.) are given to the guinea-pig intraperitoneally, a gradual fall of temperature from 38.5-28.5 degrees may be observed in the course of two hours. The animal usually recovers, and the following day the temperature is again about 38 degrees (Dale and Laidlaw). Very small doses, on the other hand, may produce a transitory rise in temperature (Pfeiffer, 1911).

In this picture is recognized the close resemblance to the syndrome produced by poisoning with so-called Witte's peptone, with Vaughan's poisonous fraction of the split protein, and to the protein intoxication following the reinjection of previously sensitized animals known as anaphylactic shock. The chief point of difference lies in the lack of coagulability of the blood brought about by the injection of peptone,

which is present only to a slight degree on the injection of histamine. Another point of similarity to anaphylactic shock is shown by the identical behavior of different species of animals to the amine as well as to the anaphylactic poison. Dogs show a much greater resistance to both forms of poisoning, the chief symptom being a gradually increasing excessive fall of the arterial blood pressure. The possible relation of histamine shock to surgical or traumatic shock is suggested by the study of the effect of this amine on the circulation in the anesthetized cat (Dale). The nonanesthetized cat tolerates large doses; it goes into collapse and coma, but recovers. If the same animal is put under an anesthetic "even moderate doses of histamine will produce a fatal circulatory collapse and respiratory failure, from which the animal does not recover even after prolonged application of artificial respiration." Analysis of this shock shows that the diminution of the output of the heart almost to the point of extinction is the principal factor of the circulatory collapse. This failing systolic output from the heart is due to inadequate filling during the diastole, the greater part of the blood collecting in the capillaries of the voluntary muscles. The fall in blood pressure is very marked, in some cases from 160 to 40 millimeters mercury; the blood viscosity, the corpuscular content and hemoglobin increase, due to loss of blood plasma and its passage into the tissues. But this "leakage of plasma from the vessels into the tissues, with the reduction in the volume and increase in the viscosity of the blood, cannot be the main cause of the shock, though it doubtless accentuates its severity. The characteristic features of the condition are not so much due to the fact that the volume of the blood is reduced, as to the tendency of what remains to stagnate in the periphery in the capillaries and venules instead of returning to the heart; this peripheral accumulation of blood is the effect of a general relaxation of the capillary vessels."

That chemical factors might be involved in the production of traumatic shock has been made probable by the work of Bayliss and Cannon, who showed that on extensive injury to the tissues of a limb, the nervous connection of which with the rest of the body has been severed, shock results; but if the blood vessels are clamped, shock is prevented. They reason that through the injury of the tissues substances are produced which on absorption into the general circulation, produce shock.

The action of histamine on the organs of the smooth muscle fiber system is best illustrated by its faculty to contract the smooth muscle fibers of the nonpregnant uterus in as small a concentration as 1 : 25,000,000. On gland cells histamine has a stimulating action eliciting on intravenous injection increased secretion of tears, of saliva, of bronchial mucus, and of gastric and pancreatic juice. If a drop of histamine solution in concentrations of from 1 : 1,000 to 1 : 100,000 is applied to the scarified skin, it produces within one minute, itching, reddening, and finally a large urticarial wheal which sends out pseudopodia-like processes and measures from 2.5-7 cm. in diameter. These wheals feel hard and resistant, are movable with the skin and cannot be removed by pressure. Subcutaneously, in doses from 0.5 to 1 mg., it produces erythema of the entire skin.

RELATION TO PHYSIOLOGY AND PATHOLOGY

The short description of the pharmacodynamic action of the two chief representatives of the proteinogenous amines will suffice to suggest the possible relationship these substances may have to human physiology and pathology. To accept this relation as a scientific fact developed on a sound basis without indulging in interesting but fruitless speculation, it is necessary to satisfy several preliminary inquiries.

1. Have these substances ever been found in the animal organism?
2. How are they formed?
3. What is their fate and function?

Before answering the first and most pertinent question, let us consider the second one. These amines were recognized as the result of putrefaction; this means they were formed from protein material by the action of micro-organisms. The bases were isolated from organs or tissues of animals, permitted to putrefy by being exposed in a haphazard way, either before or during experimentation to the ubiquitous micro-organisms, or organic material was for this purpose inoculated with a piece of putrid meat, most frequently with pancreas. Some of the workers in this field, recognizing the relation of the putrefactive amines to the amino acids, subjected a single amino acid to the action of bacteria and in this way gained a clearer insight into the chemistry of the process. The bacteria involved in this process remained obscure. In 1912, Berthelot and Bertrand isolated in pure culture from the human intestine a micro-organism which had all the characteristics of

the bacillus mucosus capsulatus (Friedländer's pneumobacillus), but in addition the faculty of decarboxylating histidine, tyrosine and tryptophane to histamine, tyramine and indolethylamine, and they therefore named this organism Bacillus aminophilus intestinalis. In the same year Mellanby and Thwort described a micro-organism belonging to the typhoid-colon group, capable of producing b imidazolethylamine from histidine. Theoretical considerations and preliminary experiments had convinced us five years ago that the ability to decarboxylate amino acids to amines could not be restricted to one or two species of bacteria, but that it might be found to be a fairly common property of micro-organisms provided that the chemical conditions of life were understood which called forth the formation of these basic products. Investigations on this problem, carried out in the Sprague Institute for Medical Research at the University of Chicago, in association with Dr. Hanke, have been published in part. We could show that the colon bacillus will form histamine from histidine only in the presence of an easily available source of carbon, such as glucose or glycerol; that the production of the amine is always coincident with the production of a medium that is distinctly acid, and we expressed the belief that the amine is formed by the micro-organism to neutralize the excess of acidity. It can therefore be accepted as a proved fact that micro-organisms, that have the faculty of forming poisonous amines from amino acids, live in the intestinal tract of man.

Can this decarboxylation of amino acids occur in the absence of micro-organisms?

The depressor action of certain organ extracts had been known for a long time. The work of Popielski had shown that such "vasodilatins" could be extracted practically from all tissues. In 1911, Barger and Dale reported that they had succeeded in isolating B imidazolethylamine from the extracts of intestinal mucosa; they showed that Popielski's "vasodilatin" contained histamine and also the depressor action of secretin of Bayliss and Starling could be explained by the presence of this base. The authors at first regarded histamine as a normal product of the intestinal mucosa, but later — under the influence of the work of Mellanby and Thwort — they adopted the view that the formation of the base is probably due to the action of bacilli.

This view is permissible, but it is extremely probable that the digestive cells of the mucosa themselves are able to decarboxylate histidine to histamine. It might be stated as a general principle that

any enzymatic activity possessed by bacteria is uniformly the property of some cells of the mammalian organism or that what the bacterial cell can do, the organ cell is able to do. If, therefore, micro-organisms possess a carboxylase activity, it is safe to assume that the multicellular organism too is possessed of this faculty of decarboxylation. In the disorder of proteinmetabolism known as cystinuria, the two diamines: putrescin and cadaverin, have been repeatedly found in urine and feces. There is no real evidence that in this condition the diamines are formed by the activity of bacteria from the two amino acids, lysin and ornithin (from arginin), and the view is generally held that the diamines, which cystinurics sometimes excrete, are the products of an abnormal protein metabolism. This conception receives very strong support through the studies of Loewy and Neuberg on a patient excreting cystin in the urine. At ordinary times no diamine could be detected in the urine, but when lysin was given to him by mouth, he excreted cadaverin in large quantities, and when arginin was given he excreted putrescin. Yet the absolute proof that the diamino acids were not decarboxylated by the intestinal bacteria, but by the cells of the organism could have been deduced only from the subcutaneous or intravenous administration of the amino acids. Unfortunately, this has not been done. Thus far it has not been definitely proved that sterile extracts or emulsions of organs like the liver harbor an enzyme of the carboxylase type, or that such enzymes are developed during the aseptic autolysis of organs.

The physiological activity of the hypophysis has been a subject of constant investigation since Oliver and Schaefer, in 1895, discovered that extracts of the gland had the power of raising blood pressure. And when it was shown, some years later, that such extracts of the pituitary body had the power of producing strong contractions of the uterus, a new agent was introduced into therapeutics. Ever since the isolation of the active principle of the gland has been attempted by biochemists, and their investigations have shown that the substance behaves like a base, the only precipitant to bring down the active principle being phosphotungstic acid. Fühner, in association with the other chemists of Meister Lucius und Bruening in Höchst am Main, claimed to have isolated four different crystalline substances, all of which showed physiologic activity in varying degree, and Fühner believes that there exist four active principles. His work, however, invites the

interpretation that these four active fractions owe their activity on the uterus to contamination, absorption or chemical combination with one and the same true active substance of exceedingly high potency.

The base precipitated from pituitary extracts gives the chemical reactions which characterize it as an imidazol derivative, and since B imidazolethylamine or histamine produces powerful contractions of the uterus, it has been considered quite possible that the active principle of the hypophysis is a polypeptid-like derivative of this base. In June, 1919, Abel and Kubota of Johns Hopkins, published a remarkable paper in the *Journal of Pharmacology and Experimental Therapeutics*, entitled: "On the Presence of Histamine (B iminazolethylamine) in the Hypophysis-Cerebri and other Tissues of the Body and Its Occurrence Among the Hydrolytic Decomposition Products of Proteins." In this communication the authors report the isolation of histamine from the hypophysis, and they consider it the plain muscle stimulating and depressor constituent of the posterior lobe of the hypophysis. They further claim to have demonstrated histamine in the gastric and intestinal mucosa, in the liver and skeletal striated muscle; having found it in Witte's peptone, they conclude that peptone shock is due to histamine and the authors are confident that the toxic principle of Vaughan's protein poison too is histamine. But this is not all of their claim. Convinced that histamine is one of the products of the enzymatic digestion of protein-containing foods, the authors make the extraordinary statement that they have obtained histamine on the acid hydrolysis of egg albumin, casein and edestin. To quote from their paper: "It is our opinion that this substance makes its appearance wherever living protoplasm exists, or at least wherever protoplasm is killed; in other words, that it arises wherever true protein is even partially disrupted by enzymes, acids or other hydrolytic agents." While such statements concerning the great importance of the amines coming from one of the foremost scientists of our country is extremely gratifying to us, who have worked on this subject now for nearly five years, we feel — on the basis of our work *— more than a little hesitancy in accepting Abel's results in their entirety. But this is not the time nor the place to debate differences of results due to differences in methods. We are in accord in our views regarding the fundamental significance of the proteinogenous amines for the physiology and pathology of the human organism. Regarding the fate of the protein-

* See our papers in the Journal of Biological Chemistry, 1920.

ogenous amines in the animal organism, we are still insufficiently informed. It could be shown by Ewins and Laidlaw that if p. oxyphenylethylamine is given by mouth to dogs, about 25 per cent. is eliminated in the urine as oxyphenylactic acid. It is known that the liver is the organ chiefly involved in this process of deamination and oxydation, for on perfusion of the surviving rabbits' liver, up to 70 per cent. of the theoretically possible acid was actually isolated. Similarly, indolethylamine is converted into indoleacetic acid on perfusion through the liver. The fate of B imidazolethylamine in the organism is still unknown. This katabolism of the amines to a fatty acid proceeds probably by way of the alcohol and the aldehyde according to the following scheme:

$$\underset{\text{I}}{RCH_2NH_2} \longrightarrow \underset{\text{II}}{RCH_2OH} \longrightarrow \underset{\text{III}}{RCH{=}O} \longrightarrow \underset{\text{IV}}{R-COOH}$$

By these transformations, these physiologically active substances are detoxicated, in the healthy organism, in the liver. Morbid conditions, then, will depend on the quantitative relationship of poisons produced and detoxicating function. The insufficiency of the detoxicating apparatus or an excessively large overproduction of amines might produce disease.

These are, in brief, some of the newer facts which the study of the proteinogenous amines has established. Their application to the more practical problems of clinical medicine, based on the use of the exact methods developed, promises a rich field. But I have deliberately abstained in my discussion from leaving the firm soil of the evidence gained by experiments to venture out on the perilous sea of supposition and speculation.

THE ORGANIZATION OF RESEARCH IN OUR AMERICAN DEMOCRACY

JAMES R. ANGELL
Chairman of the National Research Council

March 5, 1920

I

Hardly had President Wilson formulated our purpose in the Great War as that of making the world safe for democracy before voices were heard here and there urging that we should also make democracy safe for the world. The close of the war, with the crushing victory of the Allies, has seen increasing significance attached to this demand, and a new and more critical insistence on a satisfactory definition of "democracy" itself. It is, however, furthest from the intention of the present paper to attempt any philosophical exposition of the conception of democracy. For the purpose in hand, democracy is simply contrasted with autocracy as designating a human order in which the component individuals in theory, at least, determine the form of organization under which the community administers its affairs, as contradistinguished from an order in which some single individual or some small self-appointed group assumes these functions. It is the place of scientific research in such a form of human organization and a consideration of the practicable methods of safeguarding and promoting in the United States the interests concerned that constitute the subject of our present discussion.

Science in general, however defined in its abstract phases, is in its practical aspects simply the organized technic of human knowledge by which the community and the individual alike sustain themselves in the face of natural forces. Scientific research is the germinating vital principle by which this technic is constantly developed to meet more fully the shifting conditions of life, and to master more perfectly the forces of the environment. To eliminate it would be tantamount to the final stagnation of human progress and the production of a condition of substantial equilibrium, a withdrawal of the fruitful operations of intelligence, and a reduction of human behavior to purely stereotyped and habitual forms. Scientific research is, accordingly, in no sense an extrinsic luxury of the mind, nor does it merely reflect the play of intellectual curiosities; it is of the very life-blood of human

progress, the embodiment of the inner principle of intelligence itself. The maintenance of appropriate and fruitful conditions for its growth is therefore in the final analysis a matter of absolutely fundamental significance for humanity, and in a democratic order of society, it requires peculiar nurture because it appeals to the full appreciation of only the highly intelligent, and consequently stands in constant danger of being underestimated, with resulting loss of adequate financial and social support.

To discuss the organization of research in a democracy presupposes an affirmative answer to a preceding question and one to which, in the minds of many persons, a negative response should be made. There are not a few individuals, and among them many persons of high intelligence, to whom the intrinsic idea of research is foreign, and indeed hostile, to all thought of organization. They regard it as the field of purely personal initiative and as depending solely on individual fertility of imagination. They think of the occasional great inventor or discoverer as working in lonely isolation with the fruits of his own genius, and in the fullness of time passing these on to an eager humanity. To surround these elect of the gods with the trammels of organization of any kind whatever appears to them to be a sort of profanation, a sacrilege in the intellectual holy of holies.

A complete and convincing rebuttal of this position is perhaps impracticable within the limits of time at our disposal, but at least a few pertinent considerations may be submitted.

In the first place, it is unquestionably true that up to the present time, science has very largely relied for its advances on the individual worker and on relatively isolated effort in research. But, on the other hand, the evidence has been rapidly accumulating that in some directions we have approached the limits of profitable investigations on this basis, and while the final contribution must always be made by the resourceful intelligence of the individual worker, it is perfectly clear, both as a matter of theory and as a matter of accomplished fact, that in vast unexplored areas, the only effective procedure involves one or another of the forms of organization. Medicine offers some of the most striking demonstrations of this fact. It is a safe prediction that whereas the past generations of modern science have been chiefly characterized by individualistic effort in research, the next epoch will be quite as definitely characterized by cooperative organizations of various types. Prior to the war there had been certain instances of

organized research, especially under government auspices, which had achieved scientific results of unquestioned value. Certain of the geological surveys may be taken to illustrate this type of thing. But the war exercised a prodigious stimulation on the imagination of scientific men, and served to exhibit with conclusive thoroughness both here and abroad the indispensable nature of far-reaching cooperation and organization, in order to solve certain of the most urgent problems presented to a nation, whether in time of war or of peace. We have, therefore, definitely passed the point at which the merits of the organization of research need to be discussed as merely hypothetical. The limits of these advantages are still, to be sure, uncertain; the methods of accomplishing them are also far from definitely determined; but there can no longer be any question of the possible values inherent in such procedure.

We come at once then to the two fundamental issues in the whole affair. First, how shall there be established some agency for the stimulation and guidance of research, determining particularly how and where profitable cooperation may be brought about; and second, how shall research be financed? These two problems hang closely together, and in discussing the one, we shall in fact be largely concerned with the other. To make our considerations profitable in the time at our disposal, we must turn at once to the existing situation. Were we setting out with a brand new social and political organization, as is now being done in certain parts of the world, we might perhaps provide differently. But as a matter of fact, there are already many research agencies in operation, and our duty is rather to examine these to determine how far they comport with democratic institutions, and in what manner, if at all, they may be made to serve more fully their true functions.

In our own democracy we are far from having determined with finality what enterprises we shall administer through explicitly government agencies, and what we shall accredit to private initiative. Of late the pendulum has undoubtedly been swinging to the side of an increasing assumption of government control over interests hitherto privately administered, but it does not at all follow that this process will ultimately eliminate all privately controlled enterprises; in other words, it does not follow that the general principles of democracy need eventuate in the extremer forms of socialism. There can be no practical doubt that for the next generation at least, the supervision

of scientific research will in large degree be left to nongovernmental agencies. Moreover, it is to be remembered that many results intrinsically based on democratic principles of procedure may be attained without employing the political instruments of democracy. The practice of medicine, for example, is generally conducted under certain regulations established by the government, but its actual conduct is, for the most part, in the hands of individuals or organizations quite separate from any political connection. The community patronizes these individuals and organizations or not, as it chooses. In this, its action comports with that freedom of personal choice so integral to all conceptions of a democracy. But the form of the action has no political significance. We may therefore assume that any process which is free from autocratic coercion, and in which the welfare of the community is given dominant consideration, complies with the democratic spirit and ideals.

II

Without pretense of literal completeness, it is safe to say that the principal research agencies in the United States are the following: (1) Federal scientific bureaus with their accessories; (2) state bureaus, experiment stations, and scientific commissions; (3) universities and professional schools; (4) privately endowed research institutes, including certain museums; (5) industrial laboratories and research organizations. This list omits the small but occasionally significant group of independent scientific workers, whose number is in this country so inconsiderable as properly to be disregarded in connection with this analysis. It also omits state and municipal academies, a few of which have some significance for research.

1. In the nature of the case, the federal scientific organizations necessarily proceed under government direction. This does not preclude their entering from time to time on cooperative relations with other organizations, but it does in general limit such cooperation to purely informal and incidental forms. The scientific achievement of any one of these bureaus is largely dependent on the character of the director, who is necessarily an appointee of the political party in power at the time of his selection. Despite certain notorious exceptions, the general caliber of these bureau chiefs has been excellent.

The history of the development of these bureaus has been one of slow growth step by step, now some energetic individual with imagination and magnetic persuasiveness inducing Congress to furnish the

necessary funds; again, some great group of vested interests insisting that the government come forward and furnish needed scientific assistance. Once established, Congress has generally been ready to continue appropriations to these bureaus, but the increase of such appropriations, which must inevitably follow a healthy growth of the work, has not been so easy to secure.

Now as a matter of democratic theory, much is to be said for alloting to the federal government the great burden of responsibility for scientific research in those fields obviously affecting the public interest. But practically, we have not yet reached a stage even approximating such conditions, and certain present limitations under which these agencies operate must be recognized.

In the first place, then, it is difficult to persuade Congress to make appropriations for branches of science which do not rather conspicuously affect the great mass of people. The niggardly appropriations which have generally been made available to our State Department reflect this spirit. It is not obvious just how the inhabitants of Fox Corners or Bear Gulch are benefited by competent representation in foreign capitals, and until it is, the average congressman is not going to be greatly interested in the matter. The same principle operates in the appropriations for science, and especially for research. It is fair to say that the more recent sessions of Congress have shown appreciable development in this matter, but the conditions are still far from satisfactory.

In the second place, and quite as important, is the fact that the scientific bureaus inevitably find themselves put under severe pressure to deal only with problems of immediate practical importance. The time of the staff of many of them is monopolized by replying to inquiries. This is all quite as it should be, if there were at the same time provision for other kinds of work. Nothing is more certain than that research work devoted purely to practical problems is sure in the long run to go stale, and to exhaust itself in petty trivialities. The great revolutionary discoveries and ideas come from the cultivation of investigations in pure science, and generally without regard to possible practical utility. No one can for a moment question the indispensable value of research in applied science, nor that investigations in this field constitute a legitimate expenditure of government funds; but the other consideration is equally true, and in the long run even more significant, to wit, that a nation which disregards the interests of

research in pure science will find itself outstripped by its competitors in the modern world. To the well-informed, there can be no question, therefore, that in the selffish interests of democracy itself, research in pure science should be a matter of the utmost solicitude; but it is equally clear that under contemporary American conditions, the amount of this work that can be done under immediate government supervision is relatively small. For this part of our general national program of research, we must, for the time being therefore, look elsewhere.

2. What has been said in the preceding paragraphs regarding the scientific enterprises of the federal government holds measurably true of the corresponding work carried on by the states. As would naturally be expected, there is a wide diversity of practice among the different states, both as regards the number and scope of these scientific undertakings, and as regards the quality of the men to whom they are entrusted. Geological surveys, public health commissions, sanitation boards, highway construction commissions, drainage commissions, and agricultural experiment stations — these will suggest some of the multifarious directions in which the state has interested itself in scientific work. Properly enough, these undertakings, like those of the federal government, have generally been conceived in the interests of immediate practical results; but as a matter of fact, a good deal of their work has necessarily been of a research character, and at times small fragments of it have been such as might reasonably be included in the ranges of pure science. In states which support universities, there is oftentimes a very intimate interrelation between these state scientific bureaus or commissions and the scientific authorities of the university. Indeed, in some cases, the university operates in a particular field as the sole scientific agent of the state. Moreover, Congress has in recent years been appropriating increasing amounts of money for the furtherance of engineering and agricultural projects, most of which are by legislation conjointly administered by the states and the federal government. There is consequently a good deal of overlapping in these state and federal interests, which for the purposes of the moment we must largely disregard.

So far as these state scientific organizations undertake research work, the limitations mentioned in connection with the federal bureaus are even more in evidence, and certain others are superadded thereto. Not only is the pressure for immediate practical results probably greater, and the tendency to take the short-sighted rather than the far-

sighted view thereby increased, but there is also, owing to the more unstable political situation, less stability of official tenure and consequently less satisfactory conditions of work. Even where the mere tenure is adequately protected by civil service regulations, the ability of the political authorities to interfere by withholding appropriations, or otherwise embarrassing the scientist, is of more serious consequence. Generally speaking, the salaries paid have been also relatively less satisfactory, and the sum total of all these influences has been the reluctance of the abler men to go into such offices.

On the other hand, there is to be set over against all this the unequivocal fact that much admirable work has emanated from these scientific agencies, that a good deal of it has been of a research character and of excellent quality, and that granted a thoroughly intelligent public opinion, there is no reason why the scientific interests of the several states should not be developed to a high degree of perfection. If the state can be taught to conceive of its university as in some sense the capstone of its scientific work, and can be induced to recognize the indispensable part played by research in pure science, as well as the value of applied science, the benefit to the community can hardly be exaggerated.

Meantime, it is quite clear that because of the often arbitrary character of the state boundary lines, there is great need for the most intimate cooperation as between the scientific agencies in adjacent states. Moreover, it is probably practicable, by a reasonable adjustment of scientific plans, substantially to reduce the expenditures undertaken by adjacent states for identical forms of scientific work. The line which separates northern Illinois from southern Wisconsin is not one which has any relation to geology, agriculture, or animal husbandry — all of them economic and scientific interests of fundamental significance for both states. Abundant other illustrations will readily suggest themselves of the same sort of thing. Clearly, it is the duty of all good citizens to promote as far as possible an intelligent public appreciation of these matters, to the end that we may rapidly pass from the present somewhat disorganized and incidental attack on our national scientific problems to the level of a well-organized, inclusive, and intelligently directed program.

3. Our universities and professional schools present a bewildering complexity of conditions, both as regards their historical development, and as regards their internal organization with reference to scientific

work. Many of the strongest of these institutions are established on private foundations, frequently under sectarian direction, while others, and this a group growing rapidly in numbers and power, are entirely dependent on the state for support. As distinguished from all other research agencies, the universities, in addition to conducting a large part of the present investigations in pure science, are also the sole sources from which trained personnel is at present derived. This double function is often overlooked, but it is of peculiar significance for our democratic institutions.

Despite the fact above alluded to, that many of these institutions derive their support from private munificence, practically all are conducted in accordance with the spirit of democratic institutions in that they are seeking, so far as they are able, to serve the real needs of the community. For our purposes, we may therefore disregard this distinction based on the sources of their income. Certainly the problem that presents itself in the state-controlled and the privately controlled institutions is, so far as concerns research, of a substantially identical character. The differences that mark off one group from another in this regard are no greater than those that separate some of the members of each group from others in the same group.

As one goes about the country visiting these institutions, it becomes apparent that they differ widely among themselves in the degree to which there is in their atmosphere any appreciation of the real importance of research and a fixed resolution to cultivate it. In an unfortunately large number, the sheer routine of instruction is so urgent, and the obligation to care for the vast numbers of students who are enrolled is so pressing, that neither resources nor leisure can be commanded to care for the needs of research. In others, the conditions are far better, but there is none in which the situation is altogether ideal.

Two great groups of needs, the one substantially personal, the other institutional, confront the scientists in these institutions, and if they be not supplied, the future of science in this country must inevitably suffer gravely. The issues are so closely related that in practice they are hardly to be severed, but they deserve a brief separate discussion.

In the first place, there is at present, with the most infrequent exceptions, no adequate provision for the research man to secure sufficient uninterrupted time for his work. This limitation is generally

combined with insufficient resources for apparatus and assistance, and with seriously inadequate salary, a difficulty from which all academic men are now suffering, but it is peculiarly disastrous in its effects at this point, because the ablest research men are certainly rarer than the men who can carry respectably the work of instruction, and the loss of a few such men from the field of science entails relatively greater permanent loss for human progress. This is but another way of saying that in general our universities have never genuinely accepted the obligation to carry on research as at all equal to the obligation to give instruction.

In the second place, there is at the moment an altogether unintelligent type of competition among universities for the development of varied forms of research. It is of course to be recognized that certain great fundamental intellectual interests must be represented in the instructional work, at least, of every institution calling itself a university or even a college. But it does not follow that each such institution should undertake to develop research in all possible lines. From no point of view can the present wastefulness in this matter be justified, and unless it be corrected by voluntary cooperative effort, it is bound to lead to enduring disadvantages, not to say disaster. Let us take, without intent to be invidious, such a field as vertebrate paleontology. The scientific importance of this branch of work no one can possibly call in question, but on the other hand, it is perfectly clear that to attempt to supply every university with the resources and the personnel for thoroughly satisfactory research work in this field would be to the last degree wasteful and absurd. Many other illustrations of a similar character will suggest themselves. The universities can hardly justify themselves, nor can the scientific men who compose their faculties do so, in the persistent demand for unlimited increase of financial resources for research until they have elaborated a reasonable program for the ditribution of responsibility for research work.

Mention was made at an earlier point of the obligation of the universities to train competent research personnel. This obligation involves not only the preparation of such personnel in requisite numbers to meet the demands of the modern community, it also implies an obligation to exercise an adequate selective process by means of which those who are properly endowed in point of intellectual power shall be attracted into research work as a profession, while the unpromising and unfit shall be eliminated.

So long as the financial and social rewards of a research career do not compare favorably with the other obvious opportunities open to men of intelligence, no devices which can be applied at the training level will solve the problem. But assuming that society has come to recognize the indispensable character of this service and to reward it appropriately, there still remains the necessity of developing adequate selective methods during the period of university training.

The common device thus far employed to attract competent men into research has been the fellowship or the paid assistantship. Both of these are sufficiently familiar to require no discussion, and it probably requires no detailed demonstration to justify the statement that neither device has proved at all adequate. Stipends for fellowships have generally been too small either to attract the ablest men or to enable them to give their undivided time to research or the preparation for research. Assistantships are, at a certain point in a research man's training, of peculiar value, but they rapidly lose their importance as training proceeds and, save in a few instances, have been too poorly paid to encourage, or in some instances even to permit, competent men to take them. Furthermore, as generally administered, both forms of aid to research workers have been given at a very early stage of their development and often before they have in any wise justified complete confidence in their final fruitfulness. There is therefore unquestioned need of some form of financial support and professional recognition for men who have already received the Doctor of Philosophy degree or its equivalent, and who are ready to carry forward into actual execution investigations to which their previous work has led them. Hitherto the common fate of men at this stage of their training has been to be diverted into impossible burdens of teaching, or equally distracting purely professional work.

An experiment is now being made by the National Research Council in the fields of physics and chemistry whose results will be watched with the greatest interest. This experiment involves the selecting of a small group of men of the general grade described above, who have given high promise of achievement in research, and subsidizing them for a period of four or five years with adequate living salaries, during which time they may give themselves wholly to scientific investigation. Out of this group it is believed there will emerge many of the most valuable contributors to the development of research in the sciences

concerned, most of whom would otherwise have been lost to the drudgery of teaching, or to the allurements of professional life, or to the industries.

. Whatever methods are in point of fact selected may well be left to the determination of those immediately in charge of our training institutions. But it is extremely important that they should feel the pressure of public opinion compelling them to face this process of stimulation and selection as an absolutely essential part of their work. One meets too frequently the attitude of complete laisser-faire, the disposition to let nature take her course and to feel little concern as to what that course may be.

4. Of late years private benefactions have not infrequently been attracted to the establishment of research institutes. These have represented a wide variety of scientific fields, for example, chemistry, geophysics, terrestrial magnetism, astronomy, botany, zoology and particularly medicine. Certain of the great museums also carry on a laudable amount of research in various branches of natural science. No one can question the extremely valuable results that have come from the work of these institutes, and in the minds of many people they have seemed to furnish the most rational solution of the problem of organized research. As contrasted with the educational institutions, workers in them are entirely free from the distractions of teaching. They are, moreover, as a rule, fairly well paid, comparing, on the whole, more than favorably in this respect with academic men. These organizations are generally administered with a fine sense of public obligation, and, unlike the state and federal bureaus and stations, many of them are quite free from pressure to pursuue investigations in applied as opposed to pure science. As an expression of the wise spontaneous expenditure of wealth, they constitute a peculiarly encouraging example of what may be expected in a democracy that leaves much to private initiative. But the disadvantages of these institutions, while less obvious than those of the other agencies already mentioned, are not less real.

In the first place, the cost of administering scientific research on any large scale is too staggering to be cared for by institutions of this type when the entire field of science is taken into account. Moreover, there are some unequivocal disadvantages for the worker in certain of them in his isolation from a wide range of scientific companionship and in his freedom from the necessity of constantly maturing for

presentation to a competent body of colleagues or students the results of his investigations. Most serious of all, perhaps, is the fact that these institutes are consumers merely of personnel. They train their own men in their own particular technic, but they do not give fundamental training; for this they are obliged to rely on the universities. In this regard they are inevitably sterile, and while this does not lessen their value from the point of view of mere scientific productivity, it does materially affect their general position among the mechanisms for the production of scientific research. They must, therefore, be regarded as highly valuable elements in the contemporary situation, but as affording in no sense a complete solution of the problem of research in a democracy.

5. There remains to be mentioned the case of the industries for which research work is of critical consequence. No small part of the conspicuous position that Germany had gained for herself prior to the war was due to the extent to which, largely through government subvention, she had fostered industrial research and had brought into intimate organic contact inventors in pure and in applied science. Taking a lesson from her book, Great Britain, Italy, Japan and Canada — to mention no others — have entered on well-considered programs of industrial research with government subsidies to back them. It is certainly high time that the United States took cognizance of this situation and prepared to meet its consequences which will inevitably be shortly apparent in a severer rivalry in the markets of the world.

Under contemporary conditions in this country one must sharply distinguish from one another two sets of quite diverse circumstances. There is on the one hand the great industrial corporation with its own research laboratories and its own staff, in some cases including hundreds of men. There is in the second place a great group of industrial enterprises that either have no scientific laboratories, or have such conducted on so meager and purely routine a level as to be of negligible consequence. There is a large amount of missionary work to be done in the first group, for, astonishing as it may seem, some of the extremely important and fundamental industries organized on a large scale have been strangely negligent of the possibilities of scientific assistance. It is in the second group, however, that the largest opportunities exist, and here one or another of the cooperative devices must probably be employed. There are at the moment several conspicuous instances of this type of thing, in which a group of com-

panies, no one of which could possibly afford to finance the operation alone, have combined to conduct a joint laboratory or to employ jointly a staff of scientists to carry on for them essential research in the industrial processes which they use. There is almost no limit to which this device can be developed and there is no question whatever but that the industries will benefit immensely by the results of such undertakings. Ultimately, the community itself is sure to benefit. The converse of this picture, assuming that the industries fail to make proper use of scientific research, is not only the stagnation of industrial enterprise itself, but also the loss of that place in the markets of the world which we have hitherto won.

There is no question in anyone's mind that under the present economic organization of society it is far better that the industries should meet the cost of research such as we have been considering. Certain research work undertaken through government auspices is capable of exploitation by the industries, and the same thing is true of not a little of the research conducted in universities. To this appropriation of knowledge and skill no one is likely to raise serious objection, but on the other hand there is equally no question that the industries should and will bear the great burden of this expense for research in applied science.

A much more interesting question concerns the extent to which the industries may be asked or expected to contribute to research in pure science. Superficially considered, the attitude of the head of a stock company who urges on his board of directors investment in scientific research can only be justified if he can with substantial conclusiveness demonstrate that such an investment will pay dividends, and do so in sufficient measure to justify the expense. While this is undoubtedly a correct estimate of the situation as it appears at first inspection, a little further consideration of the matter will lead to a broader and somewhat revised verdict. In the first place, it is perfectly clear that the personnel required in the scientific work of the industries can only be recruited from the universities and technical schools. There is therefore resting on the industries a purely selfish obligation, leaving alone any more generous conception of their obligation to the community as a whole, to aid in the support of the institutions from which they secure their scientific staff. But more important still is the consideration that while no one can predict the practical value of any particular discovery in pure science, it can be conclusively shown that only

through investigations in pure science is large and constant progress in the technic of industrial processes to be secured. While it might therefore be difficult to make a good case for the demand on any isolated industry taken alone to give support to researches in pure science, a strong case can be made for the duty, as well as for the demands of merely selffish interest, of the industries as a whole to support such research. This conclusion follows almost inevitably if one conceives of the industries as subserving an essential function in the life of a democratic community, intead of conceiving them, as is so often done, as representing merely the improvement of opportunities to exploit this community. Wise and liberal-minded leaders of the great industries are already coming to take this wider and more far-seeing view.

III

The institutions and organizations that have now been discussed are those in which the actual work of research is for the most part conducted in this country. There is, however, another group of agencies, whose personnel is substantially identical with that of the groups previously mentioned, which nevertheless occupies a distinctly unique position in its relation to the promotion of research. I refer to the scientific societies, some of which are explicitly dedicated to the furtherance of research interests and practically all of which have at one time or another concerned themselves with these interests. Their activities cover a wide range, at one extreme perhaps being characterized by occasional meetings of a dominantly social character, and at the other extreme by the subsidizing and administration of definite pieces of research. We have had for many years in this country a federation of these scientific societies, the American Association for the Advancement of Science, which has by no means been inclusive of all, but which has possessed representatives from a very broad field. Similar organizations exist in other countries, and reflect the general modern recognition of a continuity of interests in all scientific work.

The personnel of societies such as these being, in theory at least, chosen for merit in the form of scientific accomplishment, evidently sustains a relation of peculiar potential value to the scientific development of our democracy. It is clear that only from this group, formed by natural processes of segregation, can be expected any considerable and uninterrupted contribution to the methods of human progress. An interesting experiment is being conducted in this country in the

effort to capitalize the energies and resources of these societies to supply certain features that are obviously lacking in our national facilities for research. I will speak of it briefly.

In the preceding chapters, I have pointed out the more obvious characteristics of our present agencies for the conduct of scientific investigation, attempting to indicate briefly their strength and their weakness. Assuming that this sketch has been essentially accurate, it will be recognized that while admirable provision is now made for research in certain of its aspects, there has been no general organization of these interests and no agency in any way responsible for their systematic development. To achieve just these ends, the National Research Council, organized during the war as a war measure, and operating under the charter of the National Academy of Sciences, has been established in perpetuity with an endowment of $5,000,000 given by the Carnegie Corporation of New York. It has also received nearly a million dollars in the last few months from other agencies, to wit, the Rockefeller Foundation, the General Education Board, the Commonwealth Fund, and a number of private individuals. The Council is built on the foundation of the national scientific societies, upward of forty being represented in its constituency. It is their instrument, so far as they choose to use it, for the promotion of research, and especially, where this is practicable and desirable, for the promotion of cooperation among research agencies. It is composed of seven Divisions of Science and Technology, including physics, mathematics, astronomy, engineering in all its branches, chemistry and chemical technology, geology and geography, medicine, biology and agriculture, anthropology and psychology. Each division is made up of scientists elected by the appropriate societies and a certain number of members at large. These men choose a chairman, who becomes a salaried officer of the Council, resident for a year or more in Washington. In conjunction with his executive committee, it is the duty of the chairman to carry out the policies adopted by his division. Working side by side with the representatives of other sciences, it is relatively easy for these chairmen to get together for cooperative work, as well as to secure criticism and suggestions on research enterprises affecting any field whatever of natural science. Most of the great scientific problems affecting the modern state or community traverse several quite distinct sciences. Public health problems afford abundant instances of this fact, running out as they do from medicine

into engineering, chemistry, bacteriology, entomology, and the like. Food, nutrition, water supply, drainage, and fuel offer countless other instances of these same overlappings of scientific problems. Under the National Research Council organization, all research work is purely voluntary. There is no coercion, no attempt to monopolize, or dictate, or in any other objectionable manner to control the individual, or the direction of his research. But on the other hand, there is brought to bear the most competent professional advice concerning the problems whose solution is most urgent, and detailed plans are formulated for the attack on such problems. Invitations are then issued to men and organizations to cooperate in the solution of such problems. If they accept, they then become part of a general scientific program, and the results which they gain are incorporated in this total project. The only kind of initiative which they lose is that which anyone abandons the moment he commits himself to one piece of work rather than another.

The Council has also a series of six so-called General Divisions, which cut across the Divisions of Science and Technology, and represent the contacts of each of these scientific divisions with some of the larger phases of the government, the state, and the life of the community. These divisions are respectively entitled Government Division, Division of Foreign Relations, Division of State Relations, Division of Educational Relations, Division of Research Extension, and Research Information Service. This is neither the time nor the place to elaborate on the functions of each of these general divisions, but a single word may be said in explanation of each.

The Government Division is made up of representatives of each of the scientific branches of the federal government, including all the technical divisions of the army and navy. It is intended to afford a medium for the informal contact of the personnel of these branches of the government service with one another, for the furnishing of a channel through which, if they choose, they may enter on cooperative scientific undertakings, and finally, a means whereby they may be brought into direct contact with the great group of nongovernmental scientific agencies.

The Division of Foreign Relations is responsible for the maintenance of satisfactory international scientific affiliations. There was held at Brussels in July, 1919, the first meeting of the International Research Council, in the formation of which our own Council had

taken a commanding part. The International Research Council will take the place of the old international unions, which were practically destroyed by the effects of the war, and the Foreign Relations Division will operate as the central clearing house for the administration of these international affairs. It will presumably be used by the State Department as its agent in many matters of international consequence.

The States Relations Division is intended to further in every possible way the interests of the organization of science inside the states, and wherever this can be done to advantage, the promotion of cooperative interests among the several states.

The Division of Educational Relations is especially devoted to the advancement of the conditions of research in the institutions of learning, with particular regard to the development of a satisfactory research personnel, and the promotion of the best conditions for research in pure science in such institutions.

The Division of Research Extension is particularly concerned with the promotion of scientific research among the industries.

The Research Information Service represents an attempt to better all of the devices by which scientific knowledge is made available for those who need to use it, not only such knowledge as is already to be found in texts and in printed documents, but also much that is not there to be found, such as the status of current researches, the location and competency of research personnel, and dozens of other facts of that kind not available anywhere in this country. The plans of this division also involve fundamental improvements in indexing, abstracting, and in the general manipulation of bibliographical materials.

It will be seen at once that any Division of Science and Technology, such as engineering, for instance, touches the work of each one of these General Divisions, so that the title of the latter does not so much indicate any lack of concreteness in the work they are doing, as it does the fact that this work touches a great range of interests.

In a democracy like our own, we enjoy the unquestioned advantages that spring from wide opportunity and the high premium put on individual initiative. In all undertakings in which these two circumstances are crucial, we outstrip all competitors. But our success is purchased at a price, and that is one which materially affects such interests as those of scientific research calling, as these do, not only for the highest forms of trained intelligence, but also for coordinated effort, on a large scale, of individuals and organizations for the most part devoid of direct relations with one another. Even a superficial

survey of the situation discloses that we need the most drastic stimulation to secure an increased social evaluation of the place of research in our national life, a greatly augmented productivity of the present research agencies, and a much more effective coordination of those agencies, both with regard to planning and with regard to executing the broad inclusive investigations required by our modern life.

The National Research Council is making a modest beginning in the effort to render the services indicated by these requirements. How well it is to succeed remains to be seen; but representing, as it does, practically all the scientific men of the country, there is no reason why, if its present organization and methods are unsatisfactory, these should not be modified and improved. In the meantime, it enjoys the prestige of a truly national basis without the limitations which are inseparable from a strictly government organization.

As a result of our analysis, we may summarize our estimate of the present situation as follows:

While the government agencies, both state and federal, supply an appreciable amount of the scientific service now required by the nation, they are materially defective on the side of research, and especially in the direction of investigations in pure science. The other agencies are moderately successful, each in its own field, but none are at all filling the needs of the community. Expansion is sadly needed in almost every direction, and especially coordination of effort. This is as true of applied and industrial scientific research as it is of the investigations in pure science. Our universities in particular need instant and radical assistance, and a wise distribution of responsibility among themselves for different kinds of research work, otherwise both the quantity and quality of research personnel will decline to a fatally low state with a consequent wreckage of research itself. This is a matter demanding the immediate attention of all patriotic citizens. In research, perhaps more than in any other interest of national consequence, it is important to stress the spirit of democracy rather than its political forms. The more it can be conducted under voluntary and unselfish auspices, the better the result, the freer and the more spontaneous its contribution. But unless it be directed with due regard to continuity and organization of effort, there will be inevitable waste and delay in the achievement of large and enduring results.

TWENTIETH CENTURY CONTRIBUTIONS TO OUR KNOWLEDGE OF THE ATOM

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I shall not enter into the discussion of controversial matters, and there are many of them in this field, but shall rather pass in simple review the extraordinary developments of the last twenty years which have thrown an enormous amount of new light on our knowledge of the atom and its behavior.

We may properly characterize the physics of the last twenty years as the physics of atomism. The physics of the last century could perhaps be characterized as primarily the physics of the ether, although the atomic theory and experimentation in the field of the atomic constitution of matter did play something of a rôle in nineteenth century developments. When, however, one remembers that the first great discovery of the nineteenth century, made in the year 1802, was the discovery by Thomas Young of the interference of light—a discovery which established the undulatory theory; and when one remembers that the most prominent name in the first half of the nineteenth century was that of Faraday, whose greatest contributions concerned the discovery of specific inductive capacities and their relations to electric charges; and when one remembers further that the most prominent name of the last half of the nineteenth century was that of Maxwell, and that Maxwell's great contributions consisted in an extraordinarily penetrating analysis of Faraday's experiments, and in the development of the theory of electric magneto waves; and when one remembers that Maxwell was followed by Hertz, who experimentally verified the Maxwell theories; and finally when one recalls that the last years of the nineteenth century were pregnant with new discoveries in wireless telegraphy, all in this same field, he begins to realize what a large fraction of our work in physics during the last century was associated with the phenomenon of the transmission of energy through space, or if you prefer, through ether. We might just as well call it ether as space in spite of the protestations of the relativists.

The twentieth century has been characterized by an entirely different group of experiments and discoveries—discoveries which have appeared at a rate altogether unparalleled in the history of the world. Most of these developments have concerned the giving up of old theories about the atom and the extension of our knowledge of atomic structure and atomic behavior. I shall try to give you a picture of what these developments have been and what is our present point of view regarding atoms, their structure and their relations to other atoms and to the phenomenon of radiation. Let me now run over rapidly a list of ten discoveries which I will call the ten most important advances of the last twenty years.

The first discovery on my list is the recent verification of the adumbrations of the Greeks regarding the atomic and the kinetic theories—the proof that, as Democritus had imagined 500 B. C., this world does indeed consist, in every part of it, of matter which is in violent motion.

Up to within ten years there were not a few distinguished scientists who withheld their allegiance even from these atomic and kinetic theories of matter. The most illustrious of them was Professor Wilhelm Ostwald, who at the world's scientific congress in 1902 publicly maintained that the facts of observation could just as well be explained without as with an atomic theory, but in the preface to a new edition of his "Outlines of Chemistry" he now says frankly:

> I am convinced that we have recently become possessed of experimental evidence of the discrete or grained nature of matter for which the atomic hypothesis sought in vain for hundreds and thousands of years. The isolation and counting of gaseous ions on the one hand . . . and on the other the agreement of the Brownian movements with the kinetic hypothesis . . . justify the most cautious scientist in now speaking of the experimental proof of the atomic theory of matter. The atomic hypothesis is thus raised to the position of scientifically well-founded theory.

I think you all know what the Brownian movements are but I wish especially to call attention to the fact that this advance was made not by a practical man, but by mathematical physicists; men who had the training, the penetration and the capacity to analyze phenomena and to develop necessary quantitative relationships between them. It is to Einstein of recent fame, to Smoluchowsky, a Pole, and to Sutherland of New Zealand to whom the credit for this advance is about equally due. The results consist in predicting, from the assumption that every particle suspended in a liquid or a gas, no matter what its

size, is endowed with exactly the same energy of random agitation, how far a given particle that you can see in an ultra microscope will drift in a given time, and our own experiments have checked this prediction to within one-half per cent. It is that sort of evidence that has convinced Ostwald of the correctness of the kinetic and the atomic theories.

The second advance is the proof of the divisibility of the atom, a proof which grew out of the discovery of roentgen rays. Let me tell you how. If you have two plates with an electric field between them, and nothing else but a monatomic gas like helium, it is found that when the field is thrown on, the helium is perfectly stagnant; but when a beam of roentgen rays is shot between the plates some of the molecules become electrically charged and begin to jump, a part of them toward the upper plate and a part toward the lower plate, where their presence can be detected by an electrical measuring instrument. What does that show? It shows that the thing which we call an atom has electrical charges as its constituents; and the history of the last twenty years in physics has consisted pretty largely in determining what are the properties of these electrical constituents.

The third discovery shows us something about what the atoms are doing. It came just a little after the discovery of roentgen rays. And here we found matter doing things we had never dreamed it could possibly do, namely, shooting off from itself chunks of matter, some of them charged positively and some negatively, with perfectly stupendous speeds, the negatives with a speed which may approach close to the velocity of light, 186,000 miles per second, and the positives with a speed of one-tenth of that, or 18,000 miles. The fact that such speeds could be imparted to projectiles of any kind was undreamed of twenty years ago. Such was the discovery of radioactivity.

The fourth discovery that I wish to mention is the discovery of the atomicity of electricity, the proof that the thing we call electricity is built up out of a definite number of specks of electricity, all exactly alike, and that what we call an electrical current consists simply in the journey along the conductor of these electrical specks, which we may call with perfect justice definite material bodies. Now, I can give you in just a word the proof of that statement. There are half a dozen ways in which it could be approached. I will mention the one with which I am most familiar, because it is the particular proof which we worked out at our laboratory.

We took round, brass plates with a field of 10,000 volts between them, with a little hole in the top plate, and we blew an oil spray above the top plate so as to get an electrically charged body just as small as we could, for we expected that the frictional process involved in blowing the spray would charge the drops, which it was found to do. We let one of those drops come into the space between the plates and then moved it up and down by an electrical field, throwing on the field as it came close to the bottom plate, and throwing it off as it approached the upper one, and so we kept that oil drop going up and down between the plates, in the hope that it would capture some of the ions which we knew existed in the air, put there by radium or other agencies. The drop met our fullest expectations as a police officer, capturing ions frequently and signaling the fact of each capture to the observer by the change in its speed in the field. For the oil drop is an electrically charged body, and in a given field it moves with a definite speed. If however it captures an ion, its charge increases or decreases, and hence its speed increases or decreases. If the charges or ions are all alike, then we can only get one particular change in speed. If the charge that is already upon it, put there by the frictional process, is built up out of these same units, then the total speed which the field will impart must be an exact multiple of the change in speed which the capture of an ion produces. In other words, if electricity is atomic in structure, you cannot get in a given field anything except a definite number speeds, which will make an arithmetical series, that is, will come up by steps, one, two, three, etc. That is exactly what we found. We have experimented with thousands of drops and scores of different substances, and they always work exactly that way. Both positively and negatively charged drops are found to act in quite the same way, showing that both positive and negative electrical charges are built up of specks of electricity. Further we can count the number of those specks, which we will call electrons, on a given drop, with the same certainty with which you can count the number of fingers that are before you now. And again since Rowland showed that an electrical current is nothing but a charge in motion, you have here the proof that the electrical current that goes through these lamps, for example, is nothing except the motion of a certain number of electrical specks through or over the filament of the lamp. Add to that J. J. Thomson's discovery made in 1881, that an electrical charge possesses inertia, the only distinguishing property

of matter, and you have made it perfectly legitimate to say that an electrical current in a wire is a definite, material, granular something which is moving along that wire.

The fifth great discovery of modern physics is the bringing forward of evidence for the electrical origin of mass. I have just said that electricity is material. Can we turn it around, and say that all matter is electrical in origin? The last is not exactly the same as the first, and it needs evidence. When we have proved that an electrical charge possesses inertia or mass we have not shown that there is no inertia in matter which is not electrical in its origin. Now we have a certain amount of evidence on this point and I wish to state what that evidence is. We can measure the inertia of the negative electron and it is found to be $\frac{1}{1845}$ of the inertia of a hydrogen atom, but the positive electron is never found with an inertia less than the inertia of a hydrogen atom. Let us consider the inertia of the negative. So long as it is moving slowly compared with the speed of light its inertia remains constant because the shape of its electromagnetic field is not appreciably distorted by its motion. But as soon as you imagine it to be moving with a speed which is close to the speed of light, that is with a speed which is nearly as great as the speed with which its own electromagnetic field can travel forward, then further change in speed will distort the field and hence change the inertia. In other words, the inertia of a charge ought to be a function of speed only when the speed approaches the speed of light. As a matter of fact, when it is from 0.1 up to 0.9 of the speed of light, you can compute just how it ought to vary. Now, by some happy chance the physicist has found negative electrons, namely, those shot off by radium, which are going with these speeds, and hence it is possible to test our theory for these particles and see whether the rate of change of their inertia with the speed checks with the theoretical value. It is found that there is such a check. This means that there isn't any inertia in those particles which does not obey the electromagnetic laws. Therefore, we have good reason for assuming that the negative electron is nothing but a disembodied electrical charge, and that its inertia is wholly of electrical origin.

Now, with respect to the positive electron, we haven't that evidence as yet, but it is obviously in the interest of simplicity to assume one kind of inertia rather than two. Further, we have a little bit of evidence of this kind, and I wish to mention what it is, because that

will furnish an introduction to my sixth important modern discovery. We have good reason to think, at any rate, that there is only one positive electron in the hydrogen atom, but that the mass, or inertia, of that positive is almost the mass of the hydrogen atom—at any rate, we never find it any less. If this inertia is all electrical then we know from theory that the charge must be more condensed in the positive than in the negative; consequently, if we are going to make the observed inertia of the hydrogen nucleus all electrical, it must be even a more dense charge, that is a smaller body, than is the negative charge. So, we first get the picture by that kind of a theory of an atom which has an extraordinarily minute single positive nucleus, and negative electrons around the outside. We first got this picture by that kind of theory but we do not depend on that theory now, because we know that the conclusion is correct. We know that the atom does consist of a body with a positive nucleus which is extraordinarily minute, and we can tell just how large it is, if we define the nucleus as the part of the atom that is impenetrable to the alpha rays of radium.

This brings me to the sixth of our discoveries, namely, the discovery of the nucleus atom. Let me give you just a brief statement of how we know that the atom is somewhat like a miniature solar system, with an extraordinarily minute nucleus, the size of the nucleus never being more than 1/100,000 part of the diameter of the atom, with a certain number of subsidiary bodies—negative electrons—which we should liken to the planets, somewhere around the outside. How do we know that is the case? We have this direct evidence. In the phenomenon of radioactivity nature takes a helium atom which is going with a speed of 18,000 miles per second, and nature shoots that atom right through a glass wall without leaving any hole behind, and without in any way interfering with the structure of the molecules of the glass. I have photographs that make the thing so clear that the wayfaring man can see it. This obviously means that the positive nucleus itself must be extraordinarily minute. Indeed the fact that the negative electron actually shoots through those hundreds of thousands of atoms without ever going near enough to any constituent of those atoms to knock any one of them out, and the fact that the positive nucleus of helium, namely, the alpha particle, shoots through even more molecules without being deflected at all from its course, causes one to wonder whether there was anything at all that is

impenetrable in the atom. Why do we say there is a nucleus there? Because direct experiment says there is. There is a certain portion of the atom which the alpha particle itself cannot penetrate. If the impact is head on, the alpha particle goes right up to the atom and then it backs straight back again. It is only rarely that this kind of a rebound happens, but Rutherford and Geiger and Marsden counted the percentage of alpha particles which goes straight on, and the percentage which comes back, and in that manner, by perfectly simple algebraic analysis that any one of you can understand, without any assumption at all except the law of inverse squares, which can hardly be called an assumption, at least so far as the attraction between the positive nucleus and the negative electron is concerned, we find how big that nucleus is. By the size of the nucleus I mean the size of that portion of the atom which is impenetrable to the alpha particles. It comes out something like 10^{-13} centimeters. The diameter of the atom is 10^{-8}. Furthermore, by counting how the deflections of the alpha particles are distributed around this sphere, which we can do directly with the aid of zinc sulphide spread over the inside of the sphere, we can obtain the number of alpha particles deflected through any given angle, and then with a little analysis of unquestionable correctness, we find how many free unit charges positive electrons there are in this exceedingly small nucleus, and it comes out approximately one half of the atomic weight.

Now, I come to another extraordinary discovery which did not merely tell us approximately how many electrons there are in the nucleus but it told us exactly how many there are, and the result checked too with the number obtained by the foregoing approximate method. This brings me to the recent discoveries in the field of roentgen rays, and I will call the seventh of the modern advances the discovery of the nature of roentgen rays, which was virtually made by Barkla in 1904. For Barkla and others had proved that there are two types of roentgen rays, first roentgen rays which consist of simple ether pulses pushed off from an electron when it changes its speed; and second so-called characteristic roentgen rays which are formed thus: When the electrons bump into a target they set something in the target into vibration, and this something sends off perfectly definite characteristic roentgen rays, which are like monochromatic light. So, we have two types of roentgen rays; pulse roentgen rays,

like white light, and monochromatic roentgen rays, like monochromatic light, such as mercury gives rise to. That is the seventh of our great modern discoveries and it must be credited chiefly to Barkla.

The eighth I will call the discovery of crystal structure by the study of roentgen rays, which is due to Laue in Munich, and Bragg, in England. The method is simply this: In the Ryerson Laboratory we analyze light by a grating which consists of a series of equally spaced lines on a reflecting or transmitting surface. With such a device we can split light up into a spectrum but we cannot thus split it up unless the width of the grating space is comparable with the wave length of the light. In the case of roentgen rays, we had no knowledge of gratings whose grating spaces were as small as the wave length of roentgen rays, in fact such gratings were unknown until Laue had the bright idea of using the regular arrangement of the atoms in a crystal for a grating to see whether that would do the work, and it did the work marvelously well. It was found that we could compute the grating space of certain crystals from the density and the atomic weight and then from the observed spectrum we could find the wave length of roentgen rays. When we know the wave length we can work backward and find the grating space for other crystals. We are now using this method for finding the positions and the arrangements of the atoms in crystalline bodies. Bragg in his book on roentgen rays and crystal structure has described this work very well. Thus a whole new field of experimentation has been opened up and is being pursued in a great many laboratories, and with particular success in some. There are almost unlimited possibilities for the physicist and the chemist in the discovery of the exact position of the atoms in any kind of crystal by this method.

The results of this discovery, as of most of the others which I have mentioned, are rather insignificant when compared with those of the ninth which I am going to mention, namely, the discovery of the relations between the elements, and the extension of our knowledge of the radiations emitted by different substances. This discovery was made by a young Englishman only 26 years old, Moseley. Moseley was killed at the age of 27, a year after he made his epoch-making discovery, and all the lives and all the interests of the eternally infamous men who made the war are not to be compared in value to the world with a hair of Moseley's head. Yet he had to be sacrificed to save a threatened civilization—a double honor to Moseley.

His discovery was this: He was analyzing the characteristic roentgen rays which are given off when any substance is bombarded with cathode rays. The experiment was in my judgment as brilliantly conceived, as carefully and skilfully carried out, and as illuminating in its results, as any which has been done in the last fifty years. He found that the atoms of all the different substances emit radiations or groups of radiations which are extraordinarily similar, but that these radiations differ as we go from substance to substance in their wave lengths. The whole discovery can be stated in this fashion: If you take the highest frequency emitted by a given atom, and if you lay down on a table a length which is equal to the square root of this frequency, and if on top of that you lay down the square root of the frequency of the atom which has the next lower frequency, and if you continue to lay down, with one group of ends together, the measured square root frequencies of all the elements that you can study, what have you? You have a flight of stairs, with perfectly definite equal treads; that is, the frequencies change by definite steps as you go from element to element. And there are only four vacant treads between the lightest element that Moseley could study, aluminum, and the heaviest one, lead, thus indicating that there are only four elements in this range which we have not already found. An extremely interesting question is, What is the greatest common divisor of this series of steps, that is, what is the top step? There are two ways to get it. One is by filling all the spaces up to aluminum with known elements in the order of their weights—we cannot investigate the lighter ones by the roentgen-ray method because their frequencies are too low; at least, we have not yet found how to investigate them. Now there are just twelve elements below aluminum, so we may put them all in, starting with hydrogen. That would make hydrogen correspond to the top step. The second way is to find arithmetically the greatest common divisor of the square root frequencies. This gives us a frequency which is within a few per cent of the highest frequency which hydrogen can produce, according to Lyman's measurements in the ultraviolet region of optical radiations. This indicates again that hydrogen is the element corresponding to the first step. All of this seems to mean three things: first, that the roentgen rays of hydrogen are just its ordinary visible radiations; second, that Moseley opened up a whole new field of radiation, beginning with the radiations of hydrogen, and extending up to a frequency $(92)^2$ or 8464 times as

high as that given by hydrogen. I have squared 92 because 92 is the number of the step corresponding to uranium, the heaviest known element, and the one having the highest frequency in its characteristic roentgen rays. Moseley's discovery means in the third place, almost certainly, that the elements are built up one from another by successively adding the nucleus of the hydrogen atom. The probable reason for the change in frequency as the nucleus takes on a stronger and stronger charge is that the electron sending off say the highest characteristic frequency is in a stronger electrical field in the helium atom, for example, than in the hydrogen atom, and so as the charge on the nucleus goes up by successive steps in going from element to element frequencies go up by corresponding steps.

We may then picture with considerable confidence this whole physical world as built up out of one positive and one negative electron. The positive electron is the nucleus of the hydrogen atom. It is very minute in comparison with the negative, but much more massive; when two free positive electrons are tied together we have the helium atom. We don't know why these positives cling together. We can assume, as an hypothesis, that there are four positives in helium which are held together by two negatives, thus leaving but two free positions as experiment indicates in the case. The assumption here is that in the nucleus one negative is capable of holding two positives. This assumption would make the nucleus of any atom contain a number of negatives equal to the atomic number and a number of positives equal to twice the atomic number. So much for a brief and incomplete sketch of Moseley's contribution to modern physics.

The last of the great discoveries of modern physics is one that I will just touch on. It is the discovery of quantum relations in photo-electricity, in roentgen rays, and in optical spectra; but here I am coming to a field which we do not know much about, which we do not yet understand, and my main motive in introducing it is to convince you that the physicist, in spite of all he knows, or thinks he knows, is a fairly modest fellow, because there are some things he knows he does not know, and one at present is the nature of radiation. However, we know some things about it that are new. For example, it is an extraordinarily interesting fact that when light of the roentgen-ray type, or indeed, light of any frequency falls on say a lithium or sodium surface, or on almost any surface, it has the property in some way of taking hold of a negative electron in the atoms of that surface

and of hurling that electron out with a perfectly definite speed, which we can measure, and which we find to be exactly proportional to the frequency of the light. That is an extraordinary phenomenon, and it is one that we explain on a kind of quantum theory which I will not attempt to go into here, because of the fact that we have not yet worked it out fully, so that I cannot tell you anything definite about it; but at any rate, the quantum constant comes out of the photo-electric effect, as shown in my own work, out of roentgen-ray work as discovered by Duane and Hunt at Harvard, and out of spectroscope work, as shown by Bohr in the beautiful theory of the atom which he has developed within the last three or four years.

I think I have brought you in this brief survey to the outmost boundaries of our present knowledge. Bring me back ten years from now, and we will know more about these quantum theories; but for the present I will stop, and close this hasty survey of the problems and successes of modern physics.

DISCUSSION

WILLIAM D. HARKINS: I wish to call your attention to two interesting facts that have been called to my mind by Professor Millikan's paper. The first of these is that of all of the ten great discoveries in physical science of which he spoke, not one was made in America, although it should not be forgotten that one of the most important of modern physical theories, that of relativity, is based on the experimental results obtained in this country by Professor Michelson; and the second is that the twentieth century of science, as he described it, covers a considerable part of the last decade of the nineteenth century. Indeed, in this decade, a new era in physical science began, for in these few years the electron was discovered, and isolated as a negative corpuscle; and roentgen rays, radioactivity, and Hertz waves were all found experimentally in the twelve years before the beginning of the present century. In the discovery and isolation of the electron the work of Crookes and J. J. Thomson, together with that of Weichert, plays the most important part, and that of C. T. R. Wilson and of H. A. Wilson is of great value.

In connection with the recent great developments in the knowledge of the structure of the atoms, the researches of J. J. Thomson and of Rutherford are the most fundamental. It is to the latter that we owe the theory that the heavier atoms are disintegrating and giving off the nuclei of helium atoms (alpha particles with a double positive charge) and negative electrons. He is also the author of what is termed the nuclear theory of the atom, which is that the atom is in a certain sense an extremely small scale solar system in which the sun is replaced by the nucleus of the atom. This nucleus carries a positive charge of electricity, and contains practically all of the mass of the atom. In the minute solar system the planets are negative electrons.

What we call a chemical element is so named according to the number of the planets in such a solar system, that is, according to the number of these planetary electrons. Thus, any electrically neutral atom in which there is only

one planetary electron is called a hydrogen atom. If there are six such electrons, it is called a carbon atom; if eight, an oxygen atom; if twenty-six, an atom of iron; if eighty-two, an atom of lead; if eighty-eight, an atom of radium, and if ninety-two, an atom of uranium. No atomic solar system thus far considered has more than 92 planets, so there are only 92 chemical elements, of which 86 have been discovered already. It is, of course, possible that future discoveries will reveal atoms with more than 92 planetary electrons.

It is of interest to consider that all of the great differences between oxygen and nitrogen, as they react in the animal body, are due to the presence of 6 planetary electrons in each atom of the former, and 7 in each of the latter; and that the great difference between hydrogen, which is present in all organic substances, and helium, which does not unite chemically with anything else, is due to the presence of 1 negative planetary electron in each atom of hydrogen, and of 2 in each atom of helium. It is found that those planetary electrons which are nearest the outside of the atom have much more to do with its chemical and physical properties, than those which are closer to the nucleus. Thus these properties seem to depend largely on how well the outer part of the atom is filled with electrons. It may be considered that the planetary electrons in an atom are arranged around the nucleus in a series of concentric spherical shells, as has been done by Lewis and Langmuir. In the first shell next outside the nucleus there are 2 planetary electrons; in the second, 8; in the third, 8; in the fourth, 18; in the fifth, 18; and in the sixth, 32. If only two shells of planetary electrons are present, the atom may be said to be complete if it contains 8 electrons in the *outer* shell, as is the case with neon, that is, the outer shell is *completely full* of negative electrons. Such a full shell is extremely stable, and will neither take up nor give off any electrons, so that the atom is incapable of undergoing chemical changes. If, however, there are only 7 negative electrons in the outer shell of the electrically neutral atom, this shell tends to take up an extra negative electron in order to complete the shell and give it 8 electrons. This taking up of an extra negative electron gives the atom a single negative charge in excess, and we say that the atom has been converted into a negative ion with one charge. Atoms of both fluorine and chlorine contain 7 planetary electrons in their outer shell, and both substances readily give negative ions. If, however, as is the case with a sodium atom (with 11 planetary electrons in all), there is only one negative electron in the outer shell, this is held loosely and tends to escape from the neutral atom, leaving a positively charged ion which has 8 planetary electrons in its outer shell. Thus, what we call negative elements are those which contain atoms in which the outer shell of electrons is nearly full, and therefore tends to complete itself; and what we call positive elements are those in which the outer shell contains so few electrons that it tends to lose the few it has.

Nothing has been said thus far as to how the planetary electrons are held around the nucleus. It is considered that the planets are held in their positions in the solar system by what is termed the gravitational attraction between the planets and the sun. In the atom the electrons seem to be held in place largely by an electrical attraction between the negatively charged planetary electrons and the positively charged nucleus. In any neutral atom the number of planetary electrons is equal to the charge on the nucleus, when the latter is expressed in terms of the net number of positive electronic charges which

it carries. Thus the positive charge on the nucleus of a chlorine atom is 17, and the chlorine atom has, therefore, 17 planetary negative electrons outside the nucleus.

It is easy to cause the planetary electrons in an atom to escape, as, for example, by simply allowing ultraviolet light to fall on the surface of a body; but the nucleus of the atom is exceedingly stable and can be broken up only by the use of energy in a high concentration. We all know that in experiments on an ordinary scale positively charged particles if brought close together exhibit a repulsion. It therefore seems somewhat peculiar to find that the positively charged nucleus, the parts of which, from this standpoint, should repel each other, has actually such an extremely high order of stability.

There is considerable evidence, which cannot be considered here, that the nuclei of all atoms heavier than that of hydrogen, are built up from positive electrons, which are the nuclei of hydrogen atoms, and that these positive electrons are bound together by negative electrons which may be called "binding electrons." These binding electrons should not be confused with the planetary electrons in the outer part of the atom, though the same negative electron might be a binding electron at one time and a cementing electron at another. While the atom is very small—of the order of 10^{-8} cm. (one ten millionth of a millimeter) in diameter—the nucleus has a diameter not much greater than that of a single negative electron, or its diameter is from a ten-thousandth to a hundred-thousandth that of the atom. The extremely high density of material in an atom nucleus may be illustrated by the statement that if one cubic centimeter of material could be made up of the nuclei of atoms tightly packed, its weight would be of the order of ten million tons, in case the dimensions of the nucleus are of the order calculated by Rutherford.

The lightest of all atoms, that of hydrogen, has a weight of 1.0077 (on the basis of oxygen as 16); while that of helium has a weight of 4; that of carbon, 12; that of fluorine, 19; that of sodium, 23, etc. It is of interest to note that these are all whole numbers with the exception of the weight of the hydrogen atom alone. We are thus forced to the conclusion that whenever a helium atom (or an atom of carbon, oxygen, fluorine, sodium, or any other complex atom) is built up from hydrogen atoms, there must be a loss of weight, and presumably of mass, in the process. This loss of mass is evidently equal to 0.76% of the hydrogen which is used up. In what form is this mass lost? If we adopt the modern point of view that mass and energy are the same, though measured in different units, an explanation of this loss is not difficult to find. Let us assume that the nucleus of a helium atom, which carries a positive charge of 2, is made up from 4 positive electrons and 2 negative electrons (4 + plus 2 — gives 2 +). Then it may be assumed that there would be an attraction between the positive and the negative electrons, but that the positive electrons would repel each other, and the negative electrons would also repel each other. The nucleus would therefore arrange itself so that the electrons of unlike sign would be close together, while those of like sign would be as far apart as possible. This is represented by the model presented in fig. 1, in which the large disks represent negative, and the small spheres, positive electrons. The electrons need not have the shape given in the model in order to have the arrangement represented.

If we suppose that a positive and a negative electron are far apart and are pulled together by the attractive forces between them, work being done, then it is apparent that the energy of the system will decrease; and this energy loss represents, according to the theory, a loss of mass, which presumably

escapes as some form of radiation. Thus there seems to be a loss of mass of 0.76%, which may be called the packing effect, whenever a complex atom is built up from positive and negative electrons, that is, from hydrogen atoms, since the hydrogen atom consists of one positive and one negative electron.

Let us now consider the stability of atoms, which means the stability of their nuclei, since if some of the negative planetary atoms escape from the outer part of the atom we say the atom is ionized, while if either negative or positive electrons escape from the nucleus, we say the atom has disintegrated. This method of speaking has been adopted because when the atom loses planetary negative electrons it easily picks them up again and returns to the state of the original atom, that is, the change is reversible, while particles lost from the nucleus have not in any case, so far as we now know, returned to its structure again. If a whole atom is to be built, containing, say 20 positive electrons, it will contain 20 negative electrons. On the other hand, in the building up of the nucleus of this atom, all of the 20 positive electrons are included, but only half this number, or 10 negative electrons, are used. This is the general rule for light nuclei—that one negative electron will bind two positive electrons, but in the heavy atoms, when the positive charge on the nucleus becomes high, the nucleus is extremely unstable unless the relative number of negative electrons is increased.

If N is taken to represent the total number of negative electrons in the nucleus, and P, that of the positive electrons, then for any value of P-N which is the net positive charge on the nucleus, there is a certain value of the ratio N/P which gives the most stable atom. As has been stated, this value is 0.5 or ½ for the light nuclei, that is, when the positive nuclear charge is small. The most abundant atoms in the earth's crust and in meteorites are those of oxygen, silicon, magnesium, calcium, and iron; and all of these, with the exception of iron, in which the value is only slightly higher, have values of N/P exactly equal to ½. In the nucleus of the uranium atom, which has the highest positive charge and the mass of all of the atoms, this ratio rises as high as 0.614. When in any nucleus the ratio N/P is higher than corresponds to a stable condition, that is, when the relative number of negative electrons is high, there is in general a tendency for the nucleus to give off negative electrons (beta particles), while if N/P is abnormally low (that is, if P/N and therefore the number of positive electrons is relatively high) there is a tendency for the atom to disintegrate by giving off positively charged, or alpha, particles.

The characteristic of the atoms of any one element, such as iron, is not that its atoms have a certain atomic weight, but that the value of P-N (which may be designated by n) or the positive nuclear charge, is the same in all of them. Thus an atom might have a nucleus containing 56 positive electrons (which would give it an atomic weight of 56) and 30 negative electrons. Since 56 — 30 is 26, and 26 is the nuclear charge characteristic of iron, this would be an atom of iron. However, another nucleus might contain 52 positive electrons, and therefore have an atomic weight of 52, and if it should happen to contain 26 negative electrons, it would also be an iron atom since as 52 — 26 is 26, the nuclear charge is the same as before. Atoms which have the same value of P-N or n, have also the same number of planetary electrons and the same chemical and physical properties, and are called isotopes.

Thus the element chlorine, which was formerly supposed to have an atomic weight equal to 35.46, is now found to consist of a mixture of two isotopes which have atomic weights 35 and 37, with probably a small percentage of

still another isotope of atomic weight 39. Although the nucleus of the first of these isotopes contains 35 positive and 18 negative electrons, the second contains 37 positive and 20 negative, and the third contains 39 positive and 22 negative electrons; all of these are now said to belong to one element, since $35-18=37-20=39-22=17$, which is the nuclear charge of chlorine.

I am trying to call to your attention that what we have called, and still call, an element is often a mixture of two or more different substances, which may be separated in the laboratory, and which are therefore much more truly elements than the 92 so-called chemical elements. The first separation of an element into such parts, which was carried out experimentally, was made by Mr. C. E. Broeker and myself at the University of Chicago, and was carried out with the element chlorine. The atomic weights of the different kinds of chlorine were determined, without separating them, by Aston at Cambridge University. It should be said that the existence of such isotopes was first recognized in radioactive elements by Soddy, Fajans, and others.

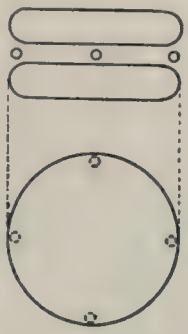

Fig. 1.—Arrangement of electrons in nucleus of helium atom.

It is now quite evident that from the standpoint of the structure of the nuclei of atoms there are at least three or four hundred elements, or what are more technically known as species of atoms; and that the atomic weight of all these pure species is always nearly a whole number on the basis of oxygen as 16 if the nucleus is complex, but is not a whole number for hydrogen in which the nucleus consists of one positive electron.

According to the theory developed by Harkins and Wilson in 1914, the most abundant constituent of all complex nuclei is the helium nucleus, with a mass of 4; there is a less abundant constituent with a mass of 3, and another with a mass of 2. All of these groups are built up of positive electrons (hydrogen nuclei) and negative electrons. All of the most abundant atoms—oxygen, silicon, iron, magnesium, calcium, sulphur, and nickel—seem to have nuclei which are built either from helium nuclei alone or with these, together with 2 negative cementing electrons in the cases of iron and nickel. The above 7 atoms make up 90% or more of all known material.

The following factors seem to give stability to an atom: (1) a low nuclear charge, (2) a normal value of N/P, and (3) the presence of an even number of negative electrons in the nucleus. The effect of factor 3 is seen in the fact that not more than one atom nucleus in 3,000 in known material contains an odd number of negative electrons. A fourth factor of importance

is that atoms which contain an even number of positive electrons are in general more stable than those which contain an odd number. Since both N and P in an atom nucleus are both usually even numbers, it is evident that P-N is also even; that is, the nuclear charge is usually an even number. The numerical value of the nuclear charge is called the atomic number. Figure 2 in which the abundance of the elements is plotted on the vertical, and the atomic number on the horizontal axis, shows clearly that the elements of even atomic number are by far the more abundant, since every even numbered element is represented by a peak and every odd numbered element by a trough.

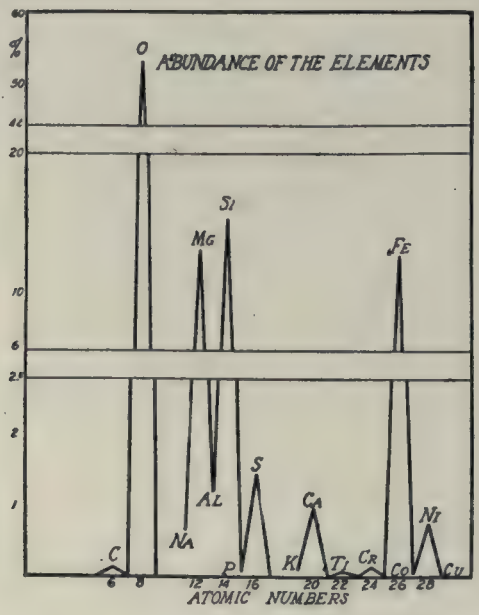

Fig. 2.—Atomic percentage abundance of the atoms in 350 stone to 10 iron meteorites, which is in the ratio of known falls. This is supposed to represent the average composition of materials as perfectly as can now be determined.

C. S. BACON: I would like to ask what has become of the ether. Has it disappeared and its place been taken by something else?

R. A. MILLIKAN, closing: I should be glad to answer, from my point of view, Dr. Bacon's question on the ether. Light and heat travel from sun to earth in some way or other. There are two hypotheses as to how they get there. One is the Newton hypothesis, the corpuscular theory, that light consists of minute particles of matter given out from a luminous body. If that is correct, any speed with which light travels must be a summation of the speed of ejection and the speed of the body which is emitting the light. The other hypothesis is that light is not corpuscular, but is a wave-motion which is propagated through space with a speed which is determined by the properties of the space and by nothing else. Of these two hypotheses, the first is abso-

lutely dead. The corpuscle theory has long been exploded and will never be revived, because we have definite experimental evidence that the speed of light bears no relation to the speed of the body emitting the light. That leaves only the second hypothesis, which is the one we have maintained for years, namely, that light and heat travel through interstellar space with a speed that has to do with the properties of the space itself. I do not care whether you call it space or ether. We have already called it ether and there is no particular sense in changing the name now. All this talk about the recent discoveries having made it necessary to modify our use of the term ether is pure folly from my point of view, because ether never had any properties except the property of transmitting electromagnetic disturbance. The whole controversy seems to me to be a quarrel over names rather than over ideas.

W. D. HARKINS: Do not some of the relativists at least indicate that light radiation consists of pulses?

R. A. MILLIKAN: What do you mean by a pulse?

W. D. HARKINS: They consider a pulse of radiated light as perhaps containing some material hurled from luminous bodies through space.

R. A. MILLIKAN: If I have a charged pithball and suddenly thrust it forward, a pulse certainly goes off through space just exactly as when I start or stop an electric current. There is no objection to the use of the term pulse. I used it in the foregoing talk. I do not think there would be any controversy on that point.

It is true, as I think you indicated, that some of the relativists seem to think that the recent discoveries in the field of physics are disastrous to the existence of ether. But from my point of view the relative theory has nothing to do with the ether. I think that is Professor Lunn's view, too. The physicists of the last century went farther than they were justified in doing in ascribing mechanical properties to the ether. All we know about ether is that there is something that transmits heat and light. We have no reason for talking about other properties. But we are going farther than our experiments entitle us to go.

SOME INFLUENCES OF FRENCH SCIENCE ON MEDICINE

THE PASTEUR LECTURE

GRAHAM LUSK

October 29, 1920

In a beautiful apartment in the Latin Quarter of Paris there lives today an elderly gentleman, the grandnephew of Lavoisier, Monsieur de Chazelles. On one wall of a salon in the apartment hangs a large painting by David of Lavoisier and his wife, both represented life size. Lavoisier, seated at his desk, has just stopped writing to turn his face toward his wife and she stands with her arm on his shoulder. Chemical apparatus are on the table and lie on the floor.

On another wall a fine portrait represents an ancestor as he appeared at the court of Louis XIV. And in the same room one finds a portrait of Benjamin Franklin which the latter sent to Lavoisier with a letter to the effect that it was one of two painted by a Frenchman then in America and that he considered them the best portraits ever made of him.

In the adjoining study of M. de Chazelles hang two drawings by Madame Lavoisier which were executed after the death of Lavoisier and retouched by David, who was Madame Lavoisier's master. These drawings represent her recollection of the first respiration experiments ever made on man. And in the desk in the same room are letters and papers of Franklin which have never been published, and which from his day to the present have been in the possession of the descendants of Lavoisier. There is a letter which contains drawings of a kite suggested to Franklin by a sailor, and a description of how he would improve it; there is an account, illustrated with drawings, of a small boat which could be propelled by forcing water from the stern by means of a piston; and there is a discussion of a suggestion that sugar was stained red with human blood, but Franklin arrives at the conclusion that when one contemplates the wars waged for the possession of the West Indies and the loss of negro slave life associated with the culture of the sugar cane, all the sugar consumed in Europe is to be considered as soaked crimson with blood.

I owe the privilege of seeing these things to my friend, Professor Jean le Goff of Paris, to whom I also owe the possession of the most important French classics on metabolism, including the sumptuous "Oeuvres de Lavoisier" published by the French government during the reign of Napoleon III. For all these treasures I am deeply grateful to him.

Lavoisier and Franklin were intimate friends, living near each other in Paris, and Franklin dined frequently with the great French chemist and his wife. In a letter written to Franklin on Feb. 5, 1790, during the early days of the French Revolution, Lavoisier says:

> After having recited what has transpired in chemistry, it is well to speak of our political revolution. We regard it as accomplished, well accomplished and beyond recall. There still exists, however, an aristocratic party which is making vain efforts but is evidently feeble. . . . We greatly regret at this moment your absence from France. You could be our guide and mark the limits beyond which we ought not to pass.

The family of Antoine Laurent Lavoisier traced its ancestry back seven generations to Antoine Lavoisier who was a post-boy in the stables of the king, and who died in 1620. Successive generations raised the position of the family name to ever higher levels until it was said of the great Lavoisier that it would require perhaps a hundred years for the appearance of his equal. Native intelligence, a fine education, great wealth, combined with the environment of the searchingly critical atmosphere of the Paris of his day, allowed of the vivid inspiration which filled his life.

Perhaps it may be fruitful to inquire into the state of chemical physiology preceding the time of Lavosier. Robert Boyle in 1660 showed that the flame of a candle or the life of an animal was extinguished after placing them in an air pump. A contemporary of Boyle, John Mayow of London, believed that air contained "nitro-aerial particles" which supported combustion and animal life. He also showed that such particles added to the weight of antimony when that metal is burned by the sun's rays and that the nitro-aerial particles contained in saltpeter, which are able to burn sulphur, are the same particles as those found in air. This was the first discovery of oxygen but it was entirely forgotten and later, when Lavoisier asked Magellan to seek for a copy of Mayow's publication, it was not to be found in any of the libraries of London.[1]

[1] Grimaux: Lavoisier, 1896, p. 107.

The German chemist, Stahl, who in 1716 moved to Berlin as physician to the king of Prussia, was the originator of the phlogiston theory of combustion, which enthralled the minds of men for nearly a hundred years. According to this theory, all combustible substances contained phlogiston which passed from them when they were burned. What we now know as oxides of iron or lead were those metals which through burning had lost their phlogiston. Such substances, if calcined with carbon, a material supposed to be rich in phlogiston, absorbed phlogiston and became metals once more. This simple theory availed to explain all the phenomena of combustion, and it was generally accepted by the scientific world.

The great physiologist, Albrecht von Haller, who died in 1777, writing his "Elementa Physiologica" [2] in the middle of the eighteenth century, has this rather hazy conception of the process of respiration:

> The secondary uses of respiration are very numerous. It exhales copiously and removes from the blood something highly noxious; for by remaining in the air it will cause suffocation; and the breath of many people crowded in a close and small place impregnates the air with a suffocating quality. On the other hand, it absorbs from the air a thin vapor of which the use is not sufficiently known.

Benjamin Franklin in "Poor Richard," 1746, thus poetically popularizes the ideas of his time:

> "Like cats in air pumps to subsist we strive,
> On joys too thin to keep the soul alive."

It must be remembered that in those days many chemists still based their ideas on the assumption of the four elements of Empedocles, air, fire, earth and water; ideas which were to be overthrown when air was shown to be a mixture of gases and water a chemical compound of gases.

One of Lavoisier's close friends was Joseph Black, professor of chemistry at Edinburgh. Black, in 1754, had found that magnesium alba, when heated, lost half its weight and that it gave off a gas when treated with acids. The gas eliminated he called "fixed air." He also found the same "fixed air" produced in fermentation, in the combustion of carbon and in expired air. Black in these experiments discovered carbonic acid.

[2] First Lines of Physiology, Trans. of Third Latin edition by William Cullen, Edinburgh, 1801, p. 131.

Nitrogen was the next gas to be revealed. In 1772, Rutherford, a friend and colleague of Black, found that when a candle was burned in an enclosed vessel until it went out and the "fixed air" was then absorbed by alkali, there remained a large volume of air which extinguished life and flame in an instant. This irrespirable gas was subsequently called nitrogen.

A year before this Priestley, in 1771, introduced a growing sprig of mint into an atmosphere in which a candle had burned out and after a lapse of several days found that another candle burned in it perfectly. Evidently the burning candle filled the space with phlogiston; the growing plant absorbed the phlogiston and produced "dephlogisticated air." This could again receive phlogiston when the second candle burned.

Shortly after this discovery (1774) Priestley submitted red oxide of mercury to the heat of a burning glass and found that an air was evolved in which a candle burned very vigorously. Priestley assumed that this air was pure dephlogisticated air, while common air was only partly dephlogisticated.

Priestley explained the presence of Black's "fixed air" in the expired air thus: "It will follow that in the precipitation of lime by breathing into lime water the fixed air which incorporates with lime comes not from the lungs but from the common air, decomposed by the phlogiston exhaled from them." And Priestley, who was one of the discoverers of oxygen, was gathered to his fathers at Northumberland, Penn., in 1804, still believing the phlogiston theory of combustion.

Independent of Priestley and before him, Scheele, a Swedish apothecary and eminent chemist, discovered oxygen by decomposing dioxide of manganese and other substances. Scheele believed that the atmosphere was composed of "spoiled air" and "fire air." When a body burned in air it lost its phlogiston, which united with "fire air." Heat consisted of "fire air" united with phlogiston. It passed through glass. In this way a portion of air could pass through glass.[3]

In 1771, Scheele [4] found that when silver carbonate was heated in a retort "fixed air" was liberated, as well as "fire air," while a residue of metallic silver remained. In 1775, he placed silver carbonate in a small retort connected with a collapsed bladder and then heated the substance. Two airs were evolved, "fixed air," which he removed with lime water, and "free air," in which a flame burned brightly. In

[3] Scheele's Briefe, p. 79, a letter of November, 1775.
[4] Physische und chemische Werke, Berlin, 1793, 1, p. 90; Briefe pp. 80, 407 and 466.

the interim between these two experiments he wrote Lavoisier in Paris a letter [5] dated Sept. 30, 1774, asking him to use his powerful burning glass on silver carbonate, then to absorb the "fixed air" in lime water and to observe whether a candle would burn and an animal live in the remaining air, and he begged Lavoisier to inform him of the results.

Scheele [6] did another striking experiment. He placed two large bees together with a little honey in a small upper chamber of a glass apparatus which he had devised. This upper chamber was in communication with a glass cylinder. He filled the glass cylinder with "fire air" and immersed its lower end in lime water. The volume of the air within the receptacle diminished day by day and the lime water which absorbed the carbonic acid rose in the tube. After eight days the bees were both dead and the lime water almost completely filled the space.

It is evident that Scheele had introduced bees into pure or nearly pure oxygen gas and that the carbon-dioxide which they produced had been completely absorbed by the lime water.

Scheele made no direct comment on this truly beautiful experiment, but in the general criticism of several experiments one may read the following hazy generalization:

> Why do not the blood and lungs change "fire air" into "acid air"? I take the liberty to express my opinion concerning this, for what would such exacting experiments profit unless through them I had the hope to more nearly approach my ultimate aim, the truth. Phlogiston, which combines with most substances, causing them to become more fluid, more mobile and more elastic, must have the same influence upon the blood. The blood corpuscles must absorb it from the air through delicate openings in the lungs. Through this combination they are expanded and in consequence become more fluid. In some part of the circulation they must give off this absorbed phlogiston and consequently be able to again absorb this fine principle when they next reach the lungs. Whither the phlogiston goes during the circulation I will leave to others to find out. The affinity of blood for phlogiston can not be as great as in the instance of plants and insects which take it from the air and also the blood cannot convert it into "acid air," but it is changed into a kind of air which is midway between "fire air" and "acid air," it is "spoiled air." For it does not unite with lime water or water as does "fire air," though it extinguishes fire as does "acid air."

Scheele's "spoiled air" was nitrogen. The poor struggling apothecary, who had made so many careful and accurate experiments and

[5] Scheele's Briefe, p. 406.

[6] Ueber Luft und Feuer, 1777, in Physische und chemische Werke, Berlin, 1793, p. 209.

who was one of the greatest chemists of his time, was unable to interpret his results without adherence to the dominant fetish of phlogiston.

We have here the picture of two earnest men, Priestley and Scheele, both absorbingly interested in chemistry, both contributing important knowledge and ranking among the greatest scientists of their day, and yet neither had the philosophical acumen to understand the meaning of their experiments. Priestley was a dissenting clergyman earning his living by preaching, but in his old age his house was burned by loyalists, and he shortly afterward fled to America. Scheele, though honored by scientific men the world over, remained a poor apothecary to the end of his days. In the current parlance of today these two great contributors to human knowledge would undoubtedly have been known outside their own circles as "narrow minded scientists."

This, however, could never have been said of Lavoisier, who repeated and extended their experiments, overthrew the phlogiston theory and established modern chemistry.

Lavoisier was elected a member of the Académie des Sciences in 1768 at the age of 24. About the same time, desirous of promoting his personal fortune, he became associated with la ferme générale, through whose activities taxes were collected in France. Some of his fellow academicians looked askance at this undertaking, but the mathematician Fontaine is reported to have remarked, "Never mind, he will be able to give us better dinners." [7]

In the ferme générale the young man was the subordinate of one Paulze, a nephew of the then all powerful Terray, minister of state and controller of finance. At the age of 28 Lavoisier married the 14 year old daughter of Paulze. His own position and his marriage brought him great wealth but in no way diminished his tireless activity. He congratulated himself that his patronage of the instrument makers of Paris had rendered France independent of Great Britain in the manufacture of scientific instruments.

Lavoisier's first paper before the Académie was "On the Nature of Water and on Those Experiments which Pretend to Prove Its Transformation into Earth." In this experiment he hermetically sealed rain water in a flask and boiled it for 101 days. Mineral matter appeared in the flask but the whole did not change in weight, and the mineral

[7] Grimaux: Levoisier, 1896, p. 32.

material that appeared was shown to be derived from the disintegration of the flask itself, which lost in weight. Lavoisier used an extremely sensitive (trés-exacte) balance, made by the official who was charged with the weighing of gold.

Here we witness the overthrow of a dogma more than two thousand years old, accomplished by the introduction of the quantitative method into chemistry. One may recall the words of Lavoisier written in his "Elements of Chemistry." [8]

> As the usefulness and accuracy of chemistry depend entirely upon the determination of the weights of the ingredients and products both before and after experiments, too much precision cannot be employed in this part of the subject and for this purpose we must be provided with good instruments. . . . I have three sets (of balances) of different sizes made by M. Fontin with the utmost nicety; and excepting those made by Mr. Ramsden of London I do not think that any compare with them in precision and sensibility.

Lavoisier had a balance which could weigh 600 gm. within 5 mg. and another which was sensitive to within a tenth of a milligram, which were quite up to modern standards of accuracy. One may visit the Conservatoire des Arts et Métiers in Paris and see there a notable collection of Lavoisier's apparatus. One sees a gasometer for the accurate measurement of gases; there is the celebrated ice calorimeter of Lavoisier and La Place; there also are barometers of finest workmanship, set in mahogany supports decorated with gilded filagree work, reminding one of the choicest furniture. These treasures were placed in the cellar of the Conservatoire during the bombardment of Paris by the Germans during the late war.

Concerning the gasometers, Lavoisier [9] wrote:

> It becomes expensive because in many experiments, such as the formation of water and of nitric acid, it is absolutely necessary to employ two of the same machines. In the present advanced state of chemistry very expensive and complicated instruments are become indispensably necessary for ascertaining the analysis and synthesis of bodies with the requisite precision as to quantity and proportion.

It is strange that Lavoisier's insistence on the use of accurate, quantitative measurements, through the application of which nearly a hundred and fifty years ago he brought about the "Chemical Revolu-

[8] Elements of Chemistry, trans. by Robert Kerr, Philadelphia, 1799, p. 375.
[9] Elements of Chemistry, Philadelphia, 1799, p. 397.

tion," should appear as new truth when enunciated by some of our ultra modern scientists.

In the heart of France near Puy-du-Dome, at Château de la Carriére, now owned by Monsieur de Chazelles, there is a veritable museum of scientific apparatus which formerly belonged to Lavoisier.[10] There are several thermometers of great accuracy and a fine balance, and there are three large glass globes, one capable of holding 15 liters of air, another 12 liters and a third 7 liters; also many other treasures of great historic value. Lavoisier made his experiments before the days when rubber and cork reduced laboratory expenses. His glass tubes and receptacles were united with finely polished brass joints.

We may imagine this accomplished Frenchman at work in his laboratory, or in his library, or receiving information from visitors to the fashionable and brilliant capital of France. It is related[11] that Priestley dined with Lavoisier in Paris in October, 1774, and informed him concerning the production of "pure dephlogisticated air" from oxide of mercury, and we may also recall that Scheele, on September 30 of the same year, wrote to Lavoisier asking him to expose silver carbonate to the heat rays of a large burning glass and produce "fixed air" and "fire air" from them.

Ten days after his conversation with Priestley, and again during the month of the following March, Lavoisier went to Montigny to visit his friend Trudaine, who was the owner of an immense burning glass 42 inches in diameter which had cost 15,000 livres (about $3,000), and here he repeated Priestley's experiments. In the paper read before the Académie des Sciences at Easter, 1775,[12] Lavoisier stated that he took the red mercury calx and heated it with carbon and obtained "fixed air," and when he heated the same without carbon a gas was evolved in which a flame burned with the splendor of phosphorus in air, and that this gas was the "air eminently respirable." The loss in weight of the mercury calx was equal to the weight of the "air eminently respirable" given off. He concluded that "fixed air" was the result of the union of carbon with "air eminently respirable."

In a subsequent paper[13] he reported that it was this "air eminently respirable" which was absorbed by phosphorus and sulphur when they burn with the production of phosphoric and sulphuric acids.

[10] Truchot: Annales de Chimie et de Physic, 1879, 18, p. 289.
[11] Thorpe: Essays in Historical Chemistry, 1902, p. 160.
[12] Oeuvres de Lavoisier, Paris, 1862, 2, p. 122.
[13] Oeuvres de Lavoisier, Paris, 1862, 2, p. 139.

Having discovered these facts, Lavoisier proceeded to determine the effect of a sparrow on the content of air in a confined space. In a brief memoire,[14] published in 1777, he enunciated the principle that during respiration it was only "air eminently respirable" (oxygen) which disappeared from the atmosphere when an animal was put into a confined space and that this air was supplanted by expired "aeriform calcic acid" (carbon-dioxide); that when metals were calcined in air oxygen was absorbed until its supply was exhausted; that if after an animal had perished in a confined space the carbon-dioxide in the atmosphere was absorbed by alkali the "foul air" remaining was the same kind of air as that found after metals had been calcined in air in an enclosed space. All the former qualities of this air could be restored by adding to it "air eminently respirable."

Three years later than this Lavoisier and La Place[15] made another step in advance. They noticed that a guinea-pig produced 224 grains of carbonic acid in ten hours and that what would now be called the respiratory quotient was 0.84. Then they put a guinea-pig in their recently constructed ice calorimeter and found that the heat given off by the animal melted 13 ounces of ice in a period of 10 hours. Next they calculated that if carbon was oxidized so that 224 grains of carbonic acid were produced, 10.4 ounces of ice would have been melted. They realized that in the case of the guinea-pig allowances would have to be made (1) because the legs of the animal became chilled during the experiment; (2) because the water of respiration was added to that of the melted ice, and (3) because the influence of cold increased the heat production of the animal. But they nevertheless stated:

> Since we have found in the preceding experiments that the two qualities of heat obtained are nearly the same, we can conclude directly and without hypothesis that the conservation of animal heat in the animal body is due at least in greater part to the transformation of "air pur" (oxygen)) into "air fixé" (carbonic acid) during the process of respiration.

Here be it noted that Lavoisier refers to the conservation of animal heat more than fifty years before the general law of the conservation of energy was enunciated. He also observed that two sparrows produced about the same quantity of carbonic acid in the unit of time as did a guinea-pig.

[14] Lavoisier: La respiration des animaux, Mém. d l'Acad. d. sc., 1777, p. 185; Oeuvres de Lavoisier, Paris, 1862 2, p. 174.

[15] Lavoisier and La Place: Mém. de l'Acad. d. Sc., 1780, p. 355; Oeuvres de Lavoisier, Paris, 1862, 2, p. 283.

About a year after these experiments (1781) Cavendish in England found that when two volumes of "inflammable air" (or hydrogen) and one volume of Priestley's "dephlogisticated air" were united by an electric spark, the airs disappeared and water resulted. Cavendish concluded that dephlogisticated air was water deprived of its phlogiston.

It is said that Lavoisier, hearing of these experiments from Blagden, secretary of the Royal Society of London, repeated them.[16] But the important point is that Lavoisier was the first really to understand the phenomenon. In a memoire presented to the Académie des Sciences in 1783,[17] he stated that water is merely a combination of "inflammable air" and oxygen and that any heat or light produced by their union is imponderable.

In the same year Lavoisier completely demolished the phlogiston hypothesis and concluded his memoire "Reflections upon Phlogiston" with the following words.[18]

> My object in preparing this memoire has been to record the new developments of the theory of combustion which I published in 1777, to show that the phlogiston of Stahl, which he gratuitously supposed existed in metals, sulphur, phosphorus and all combustible substances, is an imaginary creation. All the phenomena of combustion and calcination are much more readily explained without phlogiston than with phlogiston. I understand that my ideas will not be suddenly adopted. The human mind conforms to a certain manner of vision and those who during a portion of their lives comprehend nature from a given point of view have difficulty in acquiring new ideas. In good time the opinions I have set forth will be confirmed or destroyed. In the interim, it is a great satisfaction for me to see that young, unprejudiced minds among those who are commencing to study science, such as mathematicians and physicists, who have a new sense of chemical truths, no longer believe in phlogiston as presented by Stahl but regard the whole doctrine as scaffolding which is more embarrassing than it is useful for the continuance of the structure of the science of chemistry.

And the wonder of it all is that the great chemists of his time outside of his own country persisted in their narrow point of view. Priestley and Cavendish refused to be converted. Scheele,[19] in 1783, wrote:

> Is it impossible to convince Lavoisier that his system will not find universal acceptance? The idea of nitric acid from nitrous air and pure air, of carbonic acid from carbon and pure air, of sulphuric acid from sulphur and pure air,

[16] Thorpe: Essays in Historical Chemistry, 1890, p. 170.
[17] Oeuvres de Lavoisier, Paris, 1862, 2, p. 334.
[18] Oeuvres de Lavoisier, Paris, 1862, 2, p. 623.
[19] Scheele's Briefe, p. 364.

of lactic acid from sugar and pure air ! ! Can one believe such things? Rather will I support the English.

Only Black, professor of chemistry at Edinburgh and the discoverer of "fixed air," saw the truth. Lavoisier wrote to Black on Nov. 13, 1790, a letter [20] composed six months after the reading of his last memoire to the Académie des Sciences. He concluded the letter with the truest French courtesy:

It is only right that you should be the first to be informed of progress in a field which you opened and in which we all regard ourselves as your disciples. We do the same kind of experiments and I have the honor to communicate to you the results of our recent discoveries. I have the honor to remain, with respectful attachment, etc.

And to this Black replied in 1791:

The numerous experiments which you have made on a large scale and which you have so well devised have been perused with so much care and with such scrupulous attention to details that nothing can be more satisfactory than the proofs you have obtained. The system which you have based on the facts is so intimately connected with them, is so simple and so intelligible, that it must become more and more generally approved and adopted by a great number of chemists who have long been accustomed to the old system. . . . Having for thirty years believed and taught the doctrine of phlogiston as it was understood before the discovery of your system, I for a long time felt inimical to the new system which represented as absurd that which I had hitherto regarded as sound doctrine, but this enmity which springs only from force of habit has gradually diminished, subdued by the clearness of your proofs and the soundness of your plan.

In reading of the overthrow of the old doctrine of the fire principle phlogiston, one must feel a throb of the impending horror of the French Revolution when one considers the statements of Marat, written in 1791. Marat at one time had declared that a flame, when placed in a confined vessel, went out because the heat of the flame suddenly expanded the air, causing such a pressure on the flame that it was extinguished. Lavoisier refuted this doctrine. Marat, "L'Ami du Peuple," under the title "Modern Charlatans," published the following:

Lavoisier, the putative father of all the discoveries that are noised about, having no ideas of his own, snatches at those of others, but having no ability to appreciate them, he quickly abandons them and changes his theories as he does his shoes.[21]

[20] Richet: Revue Scientifique, 1887, 39, p. 193.
[21] Grimaux: Lavoisier, 1896, p. 207.

Certainly words of unqualified, contemporaneous disapproval!

Lavoisier's new system of salts and oxides led him to forecast the discovery of sodium and potassium, for in his "Elements of Chemistry" [22] he wrote: "It is quite possible that all the substances we call earths may be only metallic oxides irreducible by any hitherto known process." A eulogist of Lavoisier has likened this to the vision of Copernicus before Galileo's invention of the telescope.

Lavoisier had now progressed so that he was able to lay the fundamental basis of modern chemical physiology. Thus, in 1785, he stated that the discrepancy between the quantity of expired carbonic acid and inspired oxygen, which he had observed in 1780, was accounted for by the fact that a part of the absorbed oxygen was utilized to oxidize hydrogen in the lungs. This oxidation would produce additional heat and account for the discrepancy between the heat directly measured from a guinea-pig and the heat calculated as being derivable from the oxidation of carbon by oxygen. It is interesting to recall that eighty years later, in 1860, Bischoff and Voit [23] still calculated the heat value of the metabolism from the heat which would be produced in burning the carbon and hydrogen elements of the metabolism.

Respiration experiments on a human being constituted the final contribution in the culmination of this great career. The work is presented by Seguin and Lavoisier [24] in the memories of the Académie des Sciences during the year 1789. In this paper the authors remark:

> This analogy between combustion and respiration did not escape the attention of the poets and philosophers of antiquity, of which they were the interpreters and spokesmen. Fire taken from the heavens, this flame of Prometheus, not only represents an idea that is ingenious and poetical but it is a true picture of the operations of nature on behalf of animals who respire; one can say with the ancients that the fire is lighted the moment a baby takes its first respiration and is not extinguished until its death.

Before giving the details of the experiments on man the authors state that a guinea-pig respired in pure oxygen and in a mixture of oxygen and hydrogen gas just as it did in ordinary air; respiration, circulation and the intensity of combustion were uninfluenced. Nitrogen had nothing to do with respiration.

[22] Lavoisier: Elements of Chemistry, Philadelphia, 1799, p. 218.
[23] Die Gesetze der Ernährung des Fleischfressers, Leipzig, 1860, p. 43.
[24] Oeuvres de Lavoisier: Paris, 1862, 2 p. 688.

In the experiments on man Seguin himself was the subject. The results were:

TABLE 1

RESULTS OF EXPERIMENTS ON MAN

Condition	Environmental Temperature, Degrees	Oxygen Absorbed per Hour
(1) Without food	26	1,210 pouces de France
(2) Without food	12	1,344
(3) With food		1,800–1,900
(4) Work (9,195 foot pounds) without food		3,200
(5) Work (9,750 foot pounds) with food		4,600

Here are the basic facts regarding metabolism. The basal metabolism was increased 10% after exposure to cold; 50% after taking food; 200% by exercise, and 300% on combining the influences of food and exercise. We now know more details and we may also calculate that Lavoisier's determination of 24 liters of oxygen absorbed per hour in this first historical experiment on the basal metabolism was 25% too high. As for the experimental plan, it is as modern as the work of today and yet it was executed 140 years ago by the first man who really understood the significance of oxygen. It is only in the last decade that the summation of the individual stimuli caused by food and muscular work and noted by Lavoisier has been verified. Lavoisier also observed a constant relation between the quantity of oxygen consumed and the rate of the pulse multiplied by the number of respirations.[25]

How Lavoisier achieved these remarkable results is not known, for the times in which he lived became too troubled to allow further work in pure science. We find, however, the following statement in the original memoire:

> It would have been impossible to accomplish these exact experiments upon respiration before the introduction of a simple, easy and rapid method of gas analysis. This service M. Seguin has rendered to chemistry.

If one turns to the report of Seguin,[26] one finds that he states that in his work with Lavoisier he used eudiometers 8 to 10 inches high and an inch in diameter in order to determine the "vital air" or oxygen in the respired air. The tube was first filled with mercury and inverted over mercury, a little of the gas to be analyzed was introduced and

[25] Letter to Black: Revue scientifique, 1887, 39, p. 193.
[26] Annales de Chimie, 1791, 9, p. 293.

then a bit of phosphorus which was later ignited by bringing a burning ember in the vicinity of the glass. The rest of the air to be analyzed was gradually admitted, and when the tube cooled the volume of the air remaining could be measured. The loss in volume represented the quantity of oxygen absorbed. Carbonic acid could then be absorbed by potash. Seguin stated that the older method, as originally introduced by Priestley, had twenty sources of error but that his method merited attention on account of the very great exactitude with which he could determine the gases which are contained in respired air.

He furthermore truly states:

> If we enter into a room containing a large number of people we immediately smell a strong, suffocating odor, but if we use eudiometers to analyze this foul air and compare it with ordinary atmospheric air we find hardly any difference in the proportions of gases which are contained in them.

After Lavoisier's death, Madame Lavoisier drew from memory the apparatus used by her husband. There are two pictures, quite dissimilar. Good reproductions are to be found in Grimaux's "Lavoisier." In both pictures Seguin sits naked in a chair, breathing through a mask into a series of globes or bell jars. In both pictures Madame Lavoisier is shown seated at a table, taking notes of the experiment. In both pictures the pulse is being counted. In one experiment a weight is placed on Seguin's instep. The arrangement of the apparatus is quite different in the two pictures. In the experiment showing Seguin at work it seems as though valves were indicated through which inspired air was received from the atmosphere while the expired air was driven through a tube into a bell jar under water. Nysten,[27] working in Paris, in 1811, described the method by which he caused tuberculous and other patients to respire through valves into a previously collapsed bag for half a minute and then analyzed the expired air by a method similar to that of Seguin.

These are the known historical facts about the apparatus used in the first respiration experiments on man, but the exact details of the method by which results were established and which still are the basis of metabolism studies are unknown.

In contemplating his results Lavoisier said:

> This kind of observation suggests a comparison of forces concerning which no other report exists. One can learn, for example, how many pounds of

[27] Archiv für die Physiologie, Berlin, 1817, 3, p. 286.

weight-lifting correspond to the effort of one who reads aloud or of a musician who plays a musical instrument. One might even value in mechanistic terms the work of a philosopher who thinks, the man of letters who writes, the musician who composes. These factors, which have been considered purely moral, have something of the physical and material which this report allows us to compare with the activities of a man who labors with his hands. It is not without justice that the French language has united under the common expression *work* the effort of the mind with that of the body, the work at the desk with the work at the shop. . . .

Thus far we have considered respiration only as a consumption of air, the same kind for the rich as for the poor, for air belongs equally to all and costs nothing. The laborer who works enjoys indeed in great measure this gift of nature. But now that experiment has taught us that respiration is a true process of combustion which every instant consumes a portion of an individual, that this combustion is greater when the circulation and respiration are accelerated and is augmented in proportion to the activity of the individual life, a host of moral considerations suggest themselves from these determinations of physical science.

What fatality ordains that a poor man, who works with his arms and who is forced to employ for his subsistence all the power given him by nature, consumes more of himself than does an idler, while the latter has less need of repair? Why the shocking contrast of a rich man enjoying in abundance that which is not physically necessary for him and which is apparently destined for the laboring man? Let us take care, however, not to calumniate nature and accuse her of faults undoubtedly a part of our social institutions and perhaps inseparable from them. Let us be content to bless the philosophy and humanity which unite to promote wise institutions which tend to bring about equality of fortune, to increase the price of labor, to assure to it just recompense, to offer to all classes of society and especially the poor more pleasures and greater happiness. Let us trust, however, that the enthusiasm and exaggeration which so readily seizes men united in large assemblies, that the human passions which sway the multitude, often against their own interest, and sweep the sage and the philosopher like other men into their whirlpool, do not reverse an outlook with such beautiful vistas and do not destroy the hope of the country. . . .

We end this memoire with a consoling reflection. To merit well of humanity and to pay tribute to one's country it is not necessary to take part in brilliant public functions that have to do with the organization and regeneration of empires. The naturalist may also perform patriotic functions in the silence of his laboratory and at his desk; he can hope through his labors to diminish the mass of ills which afflict the human race or to increase its happiness and pleasure; and should he by some new methods which he has opened up prolong the average life of men by years or even by days he can also aspire to the glorious title of benefactor of humanity.

These are words written by the greatest scientist of his day under the spell of the French Revolution. They are words of an educated, cultivated man of middle age, spoken in the Académie des Sciences in the year of the fall of the Bastile and at a time when Edmund Burke

from the other side of the Channel said: "In the groves of their Academy at the end of every vista you see nothing but the gallows."

And in 1790, a year later, Lavoisier [28] concluded his last scientific communication to the Académie with these words:

> Up to the present time we have learned only to conjecture as to the cause of a great number of diseases and as to the means of their cure. Before hazarding a theory we propose to multiply our observations, to investigate the phenomena of digestion and to analyze the blood both in health and in disease. We will draw upon medical records and the light and experience of learned physicians who are our contemporaries and it will be only when we are thus completely armed that we will dare to attack a revered and antique colossus of prejudice and of error.

No person of understanding can escape a thrill at this vision of modern medicine expressed by him who had overthrown phlogiston, discovered the composition of the air and its relation to combustion and to life, and who had created calorimetry and revolutionized the whole of chemical thought.

True to his enthusiasm we find him drawing up the conditions for an international prize of 5,000 livres offered by the Académie des Sciences in 1792 to the author of the best experimental treatise on the liver and the bile.[29]

Lavoisier's life outside his laboratory had been that of a public official, a tax gatherer, and he had also been associated with the national manufacture of gunpowder, the quality of which he had greatly improved. He purchased a large landed estate and made experiments in scientific agriculture, doubling the wheat crop, quintupling the number of beasts on the land and earning thereby the enduring gratitude of the peasants.

However, as stated before, he had incurred the bitter hatred of Marat, and he was a tax gatherer. In November, 1793, he was arrested in his laboratory at the Arsenal, on which he had spent a large portion of his fortune. A little while before, in August of the same year, the Académie des Sciences had been closed as inimicable to the welfare of the state. This institution had been established in 1666 by Louis XIV who, after the peace of the Pyrenees, in the fulness of his power, felt that his kingdom needed nothing further than to be fortified by science, industry and art, and he intrusted his minister

[28] Oeuvres de Lavoisier, Paris, 1862, 2 p. 704.
[29] Oeuvres de Lavoisier, Paris, 1862, 6, p. 33.

Colbert to carry out his desires.[30] But les amis du peuple are notoriously suspicious of the "intelligenzia," and the Académie was abolished.

Just prior to his execution Lavoisier wrote to a friend:

> I have had a sufficiently long career, always a very happy one, and I believe that my memory will be thought of with some regret and perhaps as having something of glory. What more could I desire? The circumstances which surround me would probably lead to an uncomfortable old age. . . . It is certainly true that all the social virtues, important services to the country, a useful career employed in promoting art and human knowledge, have not sufficed to save me from a sinister end or to prevent me from perishing as a criminal.

One of the charges against Lavoisier was that he had allowed the collection of taxes on the water contained in tobacco. On May 8, 1794, at the age of 50 years, he was tried and found guilty. Twenty-eight fermiers-generaux were executed in the Place de la Republique at the same time. He witnessed the execution of his father-in-law, Paulze, who was fourth on the list, and he was the fifth upon whom the ax of the guillotine fell.

Such was the Terror.

His friend, Lagrange, whispered that night to an intimate, "It took but an instant to cut off his head; a hundred years will not suffice to produce one like it!"

Writing a hundred years later, Berthelot [31] exclaimed:

> It is our right to admire the positive work which he accomplished. The universal judgment of the civilized world increasingly reveres his establishment of chemistry, one of the fundamental sciences, upon a fixed and definite basis. There is no grander accomplishment in the history of civilization and hence the name of Lavoisier will live forever in the memory of humanity.

It is interesting to consider the differences in the lives of the men concerned in the great discoveries of the last quarter of the eighteenth century. Priestley, an indigent clergyman; Cavendish, of whom it was said that he was the most wealthy of learned men and the most learned of the wealthy; Scheele, a poor Swedish apothecary; and Lavoisier, a man of affairs, a noble of high social position in receipt of huge personal revenues. What is it, then, that makes for greatness in science? Would Lavoisier have accomplished more had he been on a "full-time" basis with a restricted income? It is a question of individual opinion,

[30] Oeuvres de Lavoisier, Paris, 1862, 4, p. 557.
[31] Berthelot: La Revolution Chimique, Paris, 1890, p. 207.

but to most people it would appear that scientific greatness depends primarily on the quality of the intellectual protoplasm of the brain, on the advantages offered to the functioning of that brain, and on the possession of a good conscience. These factors and not a coerced limitation of income are the driving forces toward the revelation of scientific truth.

Let us pass from the Paris in which Lavoisier was executed to the Paris which Liebig visited about a quarter of a century later. In the interim Napoleon had come and gone. Berthollet, an associate of Lavoisier, had taught Napoleon chemistry. Berthollet and Monge, the mathematician, had organized a company of one hundred scientists to accompany Napoleon to Egypt. Pasteur,[32] in looking into certain records, found that after Waterloo Napoleon, conversing with Monge at the Elysée, said: "Condemned now no longer to command armies, I see only Science with which to occupy my mind and my soul."

In the year 1823 Berzelius lived in Sweden, Davy in England, Volta in Italy, but in Paris lived Laplace, Berthollet, Guy Lussac, Thénard, Cuvier, Ampère and Magendie. Thorpe,[33] today president of the British Association for the Advancement of Science, writes:

> That constellation has set—
> "the world in vain
> Must hope to look upon their like again."

Into this circle both Liebig and Dumas were introduced by Alexander von Humboldt. Liebig, dedicating a French edition of one of his books to Thénard, a former master, thus expresses his appreciation:

To Monsieur le Baron Thénard,
Member of the Académie des Sciences:

Monsieur:

In 1823 when you presided over the Académie des Sciences a young foreign student came to you and begged you to advise him concerning the fulminates which he was then investigating.

Attracted to Paris by the immense reputation of those celebrated masters whose glorious researches established the foundations of the sciences and elevated them into an admirable edifice, he had no other introduction to you except his love of study and his fixed desire to profit from your teachings.

You bestowed on him a most encouraging and flattering welcome, you directed his first researches, and through your influence he had the honor to communicate them to the Académie.

[32] Vallery-Radot: The Life of Pasteur, 1902. 1, p. 257.
[33] Essays in Historical Chemistry, 1902, p. 328.

It was the session of the 28th of July which decided his future and opened a career in which for seventeen years he has labored to justify your benevolent patronage.

If his labors have been useful, it is to you that science is indebted for them, and he feels obliged to express publicly to you his ineffaceable sentiments of gratitude, esteem and veneration.[84]

JUSTUS LIEBIG.

Giessen, 1 January, 1841.

This was also the day of the French clinician Pierre Charles Alexandre Louis, whose American pupils included Oliver Wendell Holmes, Gerhard, the Shattucks and the Jacksons.

In the following years the brilliant Dumas, single handed in France, was continually entering the lists against his more methodical contemporaries, Liebig, Wöhler and Berzelius.

At the time Liebig and Dumas began their scientific carrers in Paris, Claude Bernard was a youth of 10 and Pasteur had been born the year before. Later, when Bernard was at the height of his intellectual power, some one asked Dumas, "What do you think of this great physiologist?" To which Dumas replied, "He is not a great physiologist. He is Physiology itself."

Pasteur was a pupil of Dumas, and when the Académie des Sciences in 1882 decided to confer a special medal on Pasteur, Dumas headed a chosen delegation and in his address to Pasteur said:

My dear Pasteur, your life has known only success. The scientific method which you use in such a masterly manner owes you its greatest triumphs. The Ecole Normale is proud of your work. France ranks you amongst her glories.

And in reply Pasteur said:

My dear Master, it is indeed forty years since I first had the happiness of knowing you and since you first taught me to love science.

I was fresh from the country; after each of your classes I would leave the Sorbonne transported, often moved to tears. From that moment your talent as a professor, your immortal labors and your noble character have inspired me with an admiration which has grown with the maturity of my mind.

In this fashion one can trace history from generation to generation. the influence of the individual master on the fruitful soil of a younger mind. The wonder working changes wrought by Pasteur have been thus expressed by Osler:

[84] Dedication to French edition of "Chimie organique appliqués á la physiologie végétale et a l'agriculture," Paris, Fortin, Masson & Co., 1841.

At the middle of the last century we did not know much more of the actual causes of the great scourges of the race, the plagues, the fevers and the pestilences, than did the Greeks. Here comes in Pasteur's great work. Before him Egyptian darkness; with his advent a light that brightens more and more as the years give us ever fuller knowledge.

Hear this cry of Pasteur [35] which followed the defeat of France in 1870 concerning "the forgetfulness, disdain even, that France had had for great intellectual men, especially in the realm of exact science." He says:

Whilst Germany was multiplying her universities, establishing between them the most salutary emulation, bestowing honors and consideration on the masters and the doctors, creating vast laboratories amply supplied with the most perfect instruments, France, enervated by revolutions, ever vainly seeking the best form of government, was giving but careless attention to her establishments for higher education.

The cultivation of science in its highest expression is perhaps even more necessary to the moral condition of a nation than to its material prosperity.

Last summer in Paris the illustrious president of the Physiological Congress of 1920, Charles Richet, in his opening address said: "Seek to understand things; their utility will appear later. First of all it is knowledge which matters." And he illustrated this by citing the investigations of Claude Bernard on the glycogenic function of the liver and the investigations of Portier and himself on the subject of anaphylaxis which they carried on with poisons of sea anemones injected into birds while they were sailing through tropical waters on the yacht of Prince Albert of Monaco.

It is well for us to learn lessons from the great masters of the past. Carl Voit, in 1890, said to me: "Die Franzosen sind ungeheur begabt aber die jeztzige traurige politische Verhältnisse drücken sie nieder." If we can only learn what the conditions are for the production of scientific men and provide such conditions, the world will gain hugely. A well-known British scientist said to me during the war:

The Greeks had no classical education but they had the two essentials of true education, first, the ability to express themselves correctly in words and second, to appreciate their own relation to their surroundings, which latter is science.

It is in this sense that Lavoisier and Pasteur brought understanding into the minds of men, and this makes it a rare honor and a privilege to speak of them in the first Pasteur Lecture.

[35] Vallery-Radot: Life of Pasteur, 1902, 1, p. 256.

DISEASES OF THE MOUTH AND GENERAL HEALTH

PRESIDENT'S ADDRESS

THOMAS L. GILMER

Dec. 7, 1920

The mouth is subject to as great a variety of diseases as any other part of the body, although their multiplicity and importance are often not fully recognized. I am venturing to invite your attention to some of these affections of the mouth in their relation to diseases elsewhere in the body, in the hope that the discussion may not only prove of interest, but that attention may be directed to some of the problems of the day which await solution, especially that related to the elimination of certain oral conditions of children which may affect their physical and mental well-being through life. Before adverting to these matters, however, I wish to discuss briefly the relation of disease of the mouth to general disease and to present certain views which, while not entirely in harmony with current opinion, are derived from my own experience.

Diseases of the mouth are either local in character or they may constitute part of the picture of general diseases, the primary lesion of which may be oral or situated elsewhere in the body.

Mucous patches and gumma of syphilis, Koplik spots of measles, the strawberry tongue of scarlet fever, and the petechial spots of purpura hemorrhagica are oral manifestation of general diseased conditions in other parts of the body. Lesions of the kidney, also, are often associated with pathologic changes in the mouth. When albumin is found in the urine of pregnant women, the gums often become hyperemic, swollen, tender and bleed easily on being touched. This condition of the gums disappears soon after parturition. The nonmalignant tumor, improperly called epulis, when found in the mouth of pregnant women, increases in size more rapidly during the later months of pregnancy, and after delivery, it decreases to about its former size.

Senile changes are always more or less reflected in the mouth by rapid wasting of the gums. Similar changes are also seen in the mouths of men past middle life who have long been subjected to the

strain of business and its attendant cares and anxieties. As a result of destruction of the gums, deep pockets are formed between the teeth in which accumulate debris from wasting tissues, together with food and bacteria. Teeth which have resisted disease up to this time, now decay rapidly on surfaces exposed within these pockets.

Secondary and tertiary syphilitic manifestations in the mouth are too well known to require more than passing mention. It is also well known that syphilis may appear primarily in the mouth, and there are a number of oral diseases which are sometimes mistaken for syphilis. Carcinoma of the mouth in its earlier stages has the appearance of syphilis, and indeed is believed in certain cases to develop on the site of previous syphilitic leukoplakia, and to add to the confusion a positive Wassermann reaction may be found. Chronically infiltrated ulcers of the buccal mucosa due to injuries caused by malposed teeth and by teeth having sharp edges are occasionally seen. These ulcers are covered with a grayish-white film which suggests syphilis. Removing or changing the relation of the teeth, or smoothing their sharp edges, brings about a cure. Gonorrheal and chancroidal infections are found in the mouth.

Leukoplakia of the mouth is an interesting disease. Evidently there are two forms. One is transitory, coming on suddenly, and disappearing without treatment; the other does not disappear spontaneously, and generally has a history which indicates that it is of syphilitic origin. Both are white in appearance, but the latter is a less intense white, and is more widely distributed over the mucous membrane.

Herpes of the mouth, commonly called canker sores, are frequently seen on the buccal mucosa. They appear suddenly and are extremely painful, and are not infrequently associated with gastro-intestinal disturbances. For some as yet unknown reason women are far more subject to them than are men. Actinomycosis is found in the mouth, and decayed pulpless teeth offer a convenient nidus for its implantation.

Another disease definitely primary in the mouth became prevalent among the soldiers during the World War. It is an infection of the gums, known as "trench mouth." Some thought this a new disease, but it had been recognized many years before, and was described in 1906, and named "acute ulcerous gingivitis." [1] Since then it has received many names. Weaver and Tunnicliff call it "ulceromembranous gin-

[1] Dental Review, 1906, 20, p. 459.

givitis." Later Tunnicliff isolated the predominating organism accompanying this disease for me and found it to be the Bacillus fusiformis. This organism is of special interest since it is so often found in various other lesions, and it frequently grows symbiotically with other organisms. Infections starting at the angle of the jaw and extending to the floor of the mouth, causing diffused cellulitis, known as Ludwig's angina, seem to be due to the streptococci, in association with this organism. Prior to the war acute ulcerous gingivitis was rarely seen. After demobilization it was prevalent for a time, having apparently been communicated in many instances by the exsoldiers to those who had not been in the army. It is now disappearing rapidly.

Hunter is of the opinion that septic mouths are the cause of what he calls "septic anemia." Glossitis or ulcers of the tongue and mucosa are practically always present at some time in the course of progressive pernicious anemia.

Neoplasms of the mouth are definitely primary there, and should be considered in this connection. Partsch has stated that 90% of all neoplasms which affect the jaws belong either to the carcinomas or sarcomas, of which the former comprise 53% and the latter 37%. It would seem that these figures are excessive, especially for the sarcomas, unless they include those benign growths, known as epulis, and the nonmalignant myeloid or giant-celled sarcoma. Epulis is a fibrous connective tissue growth with some of the histologic appearances of giant-celled sarcoma. Epithelioma and the malignant sarcoma are prevalent in the mouth, and the former apparently is becoming more common. Most pathologists believe that chronic mechanical irritation plays an important rôle in the causation of epithelioma, and there is evidence in favor of this belief, but my experience, which may have been unusual, indicates that the importance of mechanical chronic irritation has been overestimated. During the past three years I have seen, in my private practice, 29 cases of epithelioma of the mouth, and of this number only 8 might supposedly be attributed to mechanical injury. Nine of the growths were associated with leukoplakia. Twenty-seven of the patients were males and two were females. My clinic histories of patients who had epithelioma are not sufficiently reliable to justify an estimate of the number of these tumors which could be attributed to mechanical injury, or to the frequency of leukoplakia as an accompaniment to them, but I am of the opinion that

they do not differ materially from those seen privately. The surgeon may be led astray by the history of these growths given by the patient. He is often told that a certain sharp tooth has caused the disease, but careful examination usually discloses the fact that the primary lesion could not, in its incipiency, have been in contact with the accused tooth. Epithelioma is not usually sensitive in its earlier stages and therefore is not noticed by the patient until the growth has extended beyond its original location. As a result of the increased development of the neoplasm, the tooth later comes in contact with the increasingly inflamed and therefore more sensitive area, and then for the first time it is noticed by the patient, who naturally attributes it to the tooth. If chronic irritation were the most common cause of epithelioma, it would seem that irritation due to nose glasses would result in this disease. I have never known a case of epithelioma which was caused by irritating nose glasses, and ophthalmologists of wide experience have informed me that they also have not known such a case. Evidence is gradually accumulating which seems to indicate that heat is a factor in the cause of cancer—not a sufficient degree to produce burns, but a rather high heat frequently applied.

Sarcoma of the mouth is not uncommon in young people and children and occasionally is seen in the mouths of older persons. The round and spindled-celled varieties in the mouth are very malignant and much inclined to form metastasis, while the giant-celled or myeloid type does not cause metastasis, and in this respect is not of itself malignant; it is, however, very destructive of bone.

Mixed tumors, largely composed of glandular structure, are found in the hard and soft palate. They are always unilaterally placed, encapsulated, and not malignant. Lipoma is found in the cheek; angioma on the lips and gums; and papilloma on the palate and other localities in the mouth. Odontoma and adimantinoma of the jaws are attributed to epithelial rests, from unatrophied parts of the cord of the enamel organ. Retention mucous cysts, in the floor of the mouth, known as ranula, also, muciperous cysts of the lips, cysts of the Bland and Nuhn gland, and dentigerous cysts are an interesting group of tumors found in the oral cavity. Stones are occasionally found in Wharton's and Stenson's ducts. Evidence seems to indicate that these calcareous deposits are formed in the salivary glands and are extruded into the ducts, where they enlarge from additions received from the

lime of the salivary secretions. Bilateral exostoses are frequently seen on the lingual surfaces of the mandible in the region of the bicuspids. Occasionally they grow to considerable size, extending from the one side toward the other until they nearly meet. A similar growth is seen in the median line of the hard palate. Their removal is rarely indicated.

Tuberculosis is generally supposed to be secondary in the mouth, due to an extension of the disease from lupus on the face or lips, or from tuberculosis of the lungs. I have seen several cases in which tuberculosis seemed to be definitely primary in the mouth. In two of these the disease had attacked the tongue. There was a soft ulcerated area with ragged undermined margins, and a surface coating of a grayish-white layer. These ulcers are extremely tender, and in this respect differ from carcinoma. Multiple miliary tuberculosis is occasionally found in the mouth, studding the surface of the buccal mucosa.

The physician's interest in diseases of the mouth was increased when our own Billings, Hunter of England, and others showed the relation between tonsils and chronic oral infections of the teeth and jaws and diseases in other parts of the body. With few exceptions their statements have been accepted in full, or in modified form, but some members of the medical and dental professions have gone far beyond the claims of either Billings or Hunter, and attribute almost every conceivable bodily ill to the teeth and tonsils, when the symptoms do not definitely point elsewhere.

The two infections of the mouth which are instrumental in causing secondary disease are chronic alveolar abscess and pyorrhea alveolaris, the latter, a disease only in the adult. Their prevalence is indicated by a study made by Dr. Arthur D. Black, of 6,000 radiographs of 600 adults' jaws, taken without reference to the condition of the teeth or health. He found 78% had either chronic alveolar abscesses or pyorrhea, 55% having alveolar abscesses and 53% pyorrhea.[2]

There are two kinds of chronic alveolar abscesses, the encapsulated or walled off variety and another kind which has no capsule. The latter is filled with infected granulation tissue, having direct communication through the lymphatics and blood vessels with the adjacent healthy bone. The dissemination of dangerous germs is more likely to occur from the nonencapsuluated variety. Chronic alveolar

[2] Jour. Am. Med. Assn., 1918, 71, p. 1279.

abscesses occasionally have sinuses opening on the gums, face and into the maxillary sinus. A large percentage of antral infections are due to abscessed teeth.

Primarily pyorrhea is a disease of the peridental membrane and, with the exception of dental decay, is the most common mouth lesion. While the greater part of the pus and bacteria from pyorrheal pockets is discharged into the mouth, there is reason to believe that some of the bacteria may enter the blood and lymph channels directly from the pus pockets. Dr. Hatton of the Research Department at Northwestern University Dental School was able to demonstrate bacteria in the walls of pyorrheal pockets, and in the peridental membrane, usually perivascular in position.[3] In addition to the open infected areas, foci of infection are found in the peridental membrane far beyond the bottom of pyorrheal pockets, the bacteria having reached these isolated positions through the lymph channels in the peridental membrane. Such infections at times develop acute exacerbations which later become chronic and remain definitely closed infected processes.

If all of the teeth in the jaws had apical abscesses, the combined infected areas would be much less than if all of the teeth were involved in pyorrhea. In addition to the dissemination of bacteria from pyorrheal pockets through the lymphatics and blood vessels during the progress of the disease, there is discharged into the mouth much bacteria-laden pus, which is swallowed. There is difference of opinion as to whether the pus and bacteria from this source cause gastro-intestinal disturbance, but reports of cures of such diseases following the elimination of extensive pyorrheal pockets, may justify the assumption that pyorrhea does contribute to gastro-intestinal disease. Oral sepsis, according to Hunter, is a potent and persistent cause of septic gastritis.[4] Hunter also believes that what he terms "septic anemia" is due to oral infection, and Osler makes similar statements.[5] Since pyorrhea offers a greater area of infection than chronic alveolar abscess, and since it may at times be a closed process, it may be a greater menace to health, and therefore, it should receive due consideration in seeking the cause of disease, the etiology of which is obscure.

When we revert to the researches of Vaughan, Koessler, Walker and others, concerning the toxicity of various proteins and their split

[3] Jour. Am. Med. Assn., 1918, 71, p. 1549.
[4] Pernicious Anaemia, p. 233.
[5] Osler and McCrae: Modern Medicine.

products and their relation to hypertension and other disturbances, the importance of infections about the teeth is still further emphasized. The fact that deep pyorrheal pockets afford easy entrance for the products of infection into the blood is not to be overlooked, and a survey of the mouth for possible lesions should be included in the medical management of all such cases.

Evidence at hand showing the relation between chronic oral infection and secondary disease is too positive for refutation, and cannot be too strongly emphasized, but the indiscriminate removal of teeth and tonsils, without positive evidence of their being the cause of secondary disease, is unwarranted and unfair to patients. Through newspaper propaganda and the claims of over-enthusiastic physicians and dentists, many people have been thrown into a state of panic, and thinking their health jeopardized by their teeth and tonsils, are requesting their removal, independent of medical advice.

Some dentists and some physicians, who have not properly considered the subject, seem to have lost all sense of perspective, as a result of having too closely focused their attention on the teeth and tonsils in seeking the cause of disease, to the exclusion of other parts of the body having equal or greater infected areas; also, by attributing certain illnesses to chronic infections which are not dependent on them. It is as unscientific to attribute all cases of neuritis and arthritis to pulpless teeth, regardless of whether they are infected or not, as to attribute all bronchial asthma to polypoid growths in the ethmoid cells. Moreover, errors are occasionally made in attributing certain diseases to abscessed teeth in cases in which a carefully taken history would have disclosed the fact that the onset of the disease antedated the death of the pulps of the teeth.

Some dentists have been led to believe that the white cell blood count, especially, varies in arithmetical progression with the number of pyorrheal pockets of a certain depth, also with the number and extent of chronic alveolar abscesses as indicated by radiographs. In my clinic, Dr. Hatton has been able to demonstrate the evident absurdity of such notions by the examinatiion of several hundred patients having alveolar abscesses, pyorrheal pockets, and other mouth diseases Leukocyte counts furnish information of value only in exceptiona. cases of mouth conditions, and the leukocyte reaction is not in any essential different from that due to infection elsewhere in the body.

Indiscriminate removal of tonsils is reprehensible, but their loss, so far as known, is inconsequential as compared with the loss of teeth.

It would be unfair to impugn the motives of some dentists who daily remove many teeth, or some rhinologists who remove many pairs of tonsils, but one naturally wonders if there is not danger of the practice becoming commercialized.

There are two terms commonly used by some physicians and some dentists, which should be eliminated, since they give erroneous impressions. These are "dead teeth" and "nonvital teeth." Usually dead or nonvital teeth are abhorrent to adjacent live tissues, and when present, eliminating forces are at once set up for their removal. What really is meant by those who improperly use these terms is not that the teeth are wholly devoid of life, but that they are pulpless.

The pulp of a tooth is the formative organ of the dentine and is transitory. If one lives to very old age it disappears; the tooth still lives since the cementum of the root receives its nutrition wholly from the peridental membrane. The death of the pulp affords opportunity for apical infection, but if the root canal of a pulpless tooth is made aseptic and is hermetically sealed, the root does not usually become infected and alveolar abscess does not follow. This refutes the statement that "all pulpless teeth are a menace to health." If the peridental membrane of a tooth is completely destroyed, the tooth becomes necrosed, and then and only then does it become a "nonvital" or "dead" tooth.

If only a limited part of the cementum about the apex of the root has been denuded of its peridental membrane, as the result of an alveolar abscess, the condition may generally be cured by disinfecting and filling the root canal, and in other cases, even though a considerable part of the cementum is denuded, it may be cured by resecting the dead cementum and draining the infected area. Prior to this operation, the root canals must be disinfected and filled. Because of anatomic reasons, resection of roots is usually restricted to the eight anterior teeth. As remarkable cures of secondary diseases dependent on abscessed teeth have been brought about by root resection and thorough drainage, as have been made by the extraction of similarly infected teeth.

There is much unwarranted, spectacular operative procedure called "surgery," which removes all adjacent osseous tissue in connection with

removal of abscessed and pyorrheal affected teeth. In some cases where there has been extensive bone destruction, operative procedures may be indicated, but ordinarily the removal of the tooth suffices. The examination of 2,000 radiographs of edentulous or partially edentulous jaws, taken for me in my clinic and private practice, in which no curettement or surgical procedures had been observed, revealed only three alveolar abscesses which had persisted after the teeth had been removed. The removal of granuloma, especially if extensive, may hasten recovery and in some instances is indicated, but too much surgery has led to diffusion of bacteria through adjacent tissues with serious results.

I might incidentally refer to the use of radiographs in connection with abscesses of the jaw. The radiograph offers means of determining the extent and location of chronic alveolar abscesses. However, it must not be forgotten that radiographs are only shadow pictures and are often deceptive. The angle of exposure materially changes the shadow, giving different representations of the same thing. If one depends wholly on radiographs to determine such conditions, he may be led to wrong conclusions. For instance, occasionally a radiograph indicates deep pyorrheal pockets which, when the mouth is examined, are not found. The gums as well as the alveolar process have become atrophied at the same time, and as a result much of the necks of the teeth are exposed, giving the appearance in the radiograph of pyorrhea, which does not exist. Occasionally the shadow of the maxillary sinus is mistaken for a cyst or abscess; the mental foramen may also be mistaken for an abscess. A knowledge of the anatomy and histology of the oral tissues, coupled with experienced observation, is necessary for the proper interpretation of radiographs of teeth.

Sir James Mackenzie [6] has well said: "Disease is rarely recognized until it has impaired the health of the individual and produced suffering; and the concentration of attention to this stage has diverted the attention from the preceding stages," and we may add, has diverted attention from the cause that led up to the preceding stages.

We must start with the child at birth and care for him until he reaches manhood, if we would save him from many of the ills of life, since it is at a comparatively early period that causes for oral sepsis begin.

[6] The Future of Medicine.

When a child is born the enamel of the temporary incisors and cuspids is nearly complete, and that of the deciduous molars is a little less than half finished, and is fully completed 7 months after birth. Owing to this early development of the protective portion of the deciduous teeth, their structure is not influenced by diseases of childhood, and therefore are usually perfect in formation and rarely irregularly placed in the jaws. With the exception of the first molars, the deposition of lime salts forming the second set of teeth does not commence until about 12 months after birth. The first molar has usually begun at birth. About this time the incisal edge of the central incisors and the cusps of the occlusal surfaces of the first molars are laid down. The enamel of the incisors and first molars is completed between the fifth and sixth years, that of the cuspids, bicuspids and second molars between the eighth and ninth years, and the third molars about the twelfth year. It is during the period of enamel formation of the second set that disease and malnutrition injuriously affect the shape and quality of these teeth, causing defects in the enamel, which definitely correspond to the stage of development of the teeth at that period. The health of the first three years of life, so often modified by illness arising from faulty nutrition, contagious disease and other infections, frequently determines that the child whose heredity would entitle him to a perfect mouth, may have to go through life a sufferer from dental caries or deformed unsightly teeth.

Observation leads me to believe that scarlet fever, measles and other eruptive febrile diseases of childhood produce more profound defects in the teeth than do other even more depressing diseases, such as rickets or congenital syphilis. The inclusion of notched and narrowed teeth in Hutchinson's triad with interstitial keratitis and labyrinthine disease, a syndrome commonly and properly attributed to congenital syphilis, is somewhat unfortunate, since not all teeth so deformed are due to syphilis, and therefore the stigma is, in certain cases, unjustly placed on parents. If notched and narrowed central incisor teeth of the second set were always due to hereditary syphilis, it would seem that the deciduous set would likewise have shown such defects in those definitely syphilitic at birth. But as a matter of fact they do not, while their counterparts in the second set developed after birth are often defective, especially if the child has had depressing diseases or suffered from malnutrition. It would seem possible, therefore, that

defective teeth seen in syphilitic children may arise from the malnutrition associated with syphilis, but not necessarily more from syphilis than from other diseases of like duration and extent.

If teeth are grooved, pitted, or otherwise malformed when erupted, these defects afford opportunity for lodgment of food debris, and for acid-forming fungi, which produce the lactic acid that attacks the enamel and later the dentine, causing decay. Unless that part of a tooth destroyed is restored by artificial means before the pulp is exposed, the pulp dies, with alveolar abscess as an almost certain sequence.

Children rarely have dental decay until they are approaching their second birthday. This seems to indicate that the change from infant diet to a mixed diet is a factor in the production of decay in children's teeth. The studies of D. J. Davis, Jackson, Moore, and others have definitely proved that improper diet has a positive injurious influence on the gums and underlying bony structure. Scurvy, which is supposed to be due to dietetic causes, profoundly affects the same tissues. With these facts in mind, we may suppose that improper feeding changes as well the secretions of the mouth, so that certain constituents which normally inhibit the growth of acid-forming fungi are lacking, or that others are supplied, which in combination with food remaining about the teeth, give the best possible medium for bacterial growth. If this is true, we may believe that since dental decay begins with the change of diet, that error in properly balancing the diet may have much to do with decay of teeth. May we not raise the question as to the probability of improper diet being fundamental as a predisposing cause in other infections about the mouth, such as pyorrhea alveolaris, a disease the etiology of which is obscure?

Doubtless there are many other factors which cause or counteract dental decay and some of the other diseases of the mouth. Heredity probably plays an important part. There are many marked characteristics in the child's mouth which are without doubt due to heredity. The resemblance in quality and shape of the teeth and jaws of children and parents is noticeable in some families. The tendency to decay is likewise noticeable. Cleft palate, hare lip, and cancer, on the other hand, I have been unable to associate with heredity.

Of the child's first teeth, the molars are most subject to decay. If these teeth are neglected and decay, their pulps become exposed and the child suffers pain from mastication, and as a result he bolts his

food, thereby throwing an unnecessary amount of work on the stomach. Later the pulps die with alveolar infection as a certain sequence, and as a result a definite channel is opened from the infected roots to the blood stream through which pass bacteria from the mouth. Any organism which may have found temporary abode in cavities of dental decay, such as tubercle bacilli, actinomyces, and possibly other infections, may pass through these channels. Reports by Fones of the Bridgeport Schools [7] and Guthrie of the New Orleans schools show definite lessening of contagious diseases among children as a result of perfect oral hygiene.[8] One cannot but surmise, however, that the improved conditions in personal hygiene, other than that of the mouth which necessarily must accompany and result from the degree of cooperation of parents and children in attaining so great dental improvement, must have been an important factor in obtaining this striking decrease in contagious disease. Dental decay, especially if situated between teeth, forms pockets into which food wedges and decomposes, with resulting pain, infected gums and peridental membrane. As the bacteria from these infected areas, in their excursion from the mouth to the stomach, pass the tonsils, some may find lodgment there and cause disease of these organs. Others pass through the lymph channels to the submaxillary lymphatics, causing lymphadenitis. These facts apply to the teeth of adults as well as to those of children. Sweitzer, in 1909, succeeded in injecting the lymphatics of the dental pulp. In 1914, Noyes and Dewey of Chicago repeated the work of Sweitzer and, in addition, succeeded in injecting the lymphatic capillaries of the submaxillary glands of the neck through the pulps of the teeth, demonstrating the continuity of lymph channels between the tooth's pulp and the submaxillary glands, through which may pass bacteria from the mouth.[9] Odenthal reports finding submaxillary glandular swellings in 99% of all children having badly diseased teeth and only 49% in those having sound teeth.[10] Gilberti showed the prevalence of tubercle bacilli in the mouth by injecting into guinea-pigs, previously subjected to the tuberculin test, emulsion of inguinal and also of cervical glands, taken from children believed to be dead of non-tuberculous disease. Of 30 animals injected with cervical gland emul-

[7] Bridgeport School Report.
[8] Jour. Am. Med. Assn., 1920, 75, p. 1245.
[9] Dental Cosmos, 62, p. 1037, 1920.
[10] Therapie des Maladies Infectieuses, p. 256.

sion, 11 died from tuberculosis. Of those injected with material from inguinal glands, only 2 died of tuberculosis.[11]

Examination of the mouths of the children of the grammar schools in the poorer districts in Chicago showed that 98% had diseased teeth. In some, the teeth were so badly decayed that their masticating surfaces were destroyed beyond repair, and in addition, there were numerous abscesses. In some, the gums were so badly infected as a result of dental neglect that pus was being discharged from one end of the dental arch to the other. Dental caries and attendant infection of the gums, together with acute and chronic alveolar abscesses, no doubt contribute to a large extent to the malnutrition, nervous disorder and delinquency among the poor children of the city. The great question before us is: What can be done to prevent such conditions? Much has been done in the Forsyth Dental Infirmary in Boston, the Eastman Dispensary in Rochester, N. Y., and by the school authorities in Bridgeport, Conn., and in other cities.

We have only 2,500 dentists in this city and 310,481 children in our grammar schools alone. If the dentists of this city should serve the school children who never receive dental attention, they would have little time left for their private practice. The situation may be relieved by a system which has proved successful in other municipalities. This system provides for the instruction of women in the care of children's teeth. They are a part of the school faculty and are on duty throughout the school year. They are known as "dental hygienists" in some cities and "dental nurses" in others. Their duties are to clean thoroughly the teeth of the school children several times a year, to examine their teeth for dental decay and the mouth for other diseases, and to tabulate conditions found. If the child is in need of dental service, he is referred to the family dentist, if one is employed; if not, he is referred to the dental infirmary. The dental hygienists also give instruction in the care of the mouth and teeth by tooth brush drills. They inspect each child's mouth at frequent intervals to find whether he has given it proper home care. School instruction in the care of teeth does not reach the child as early in life as it should to secure the best results, but instruction of the grammar school children in the care of their teeth will tend to educate both the parents and younger children of the family in the importance of better habits of oral clean-

[11] Medical Practice Series, 1910, 3, p. 313.

liness. An effort is being made by the Social Service Bureau of Chicago to introduce oral hygiene into the day nurseries.

This work can be carried on in the most complete manner only under school board and municipal authority. The employment of dental hygienists in sufficient numbers to care properly for the pupils in all of Chicago's grammar and parochial schools would call for a heavy financial outlay, but when the gain in mental and physical condition is considered, it would seem that the state can well afford it. By putting this system into practice, the teaching force may be materially decreased, because it has been found that children who have been generally delinquent on account of diseased mouth conditions, make their grades easily, and in some instances make double promotions, after their mouths have been restored to health. The education of women to act as dental hygienists can most economically and conveniently be accomplished in the already existing dental schools, since these schools have the facilities, including teaching force and clinical material necessary for their instruction.

During the past twelve months several papers have appeared in prominent medical journals, relating to delinquency and nervous disorders in children, but in none of these was mention made of oral infection as a possible cause, though dietetics, heredity and environment were cited as etiologic factors.

We hear much of preventive medicine, but preventive dentistry must be intimately associated with preventive medicine if we would eliminate some of the more common causes of disease. Preventive medicine has not generally included hygiene of the mouth in its work and so has missed one of the most promising avenues of attack on fundamental causes of disease. Many corporations, however, have grasped the idea that unclean, unhealthy mouths are detrimental to health. The Metropolitan Life Insurance Company in its "Daily Bulletin" of April 29, 1919, says, "The services rendered by the Dental Division since its establishment in 1915, have been so curative of impaired health conditions and so permanently helpful to the employees who have taken advantage of the opportunities offered, that henceforth every Home Office will require its employees to undergo examination and cleansing of the teeth, in the Home Office, Dental Division, twice a year."

All boards of health should have one member who is a high grade dentist to superintend a corps of dentists and dental hygienists who care for the mouths of children in the grammar schools. Owing to the extension of time now demanded for the education of dentists and the requirementts of one year of college as a requisite for entrance to dental schools, there will not be as many dentists in the United States two years hence as there were a year ago, since death and voluntary retirement from practice will more than offset the number graduating in this time. There are only 48,000 dentists in the whole country, a number wholly inadequate to dental needs, if all the people recognized the importance of oral health.

We have been slow to recognize the importance of clean healthy mouths and consequently dentists have not been able to exert an influence as beneficial as they might otherwise have exerted. When we are all brought to realize fully that unhealthy mouths are a prolific cause of ill health then, and only then, will a systematic effort be made which will bring about correction of present neglect. Dentists must play an ever increasing rôle through the care of the mouth in the prevention of disease.

THE LITERARY VALUE OF HUNGER

CHARLES B. REED

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"Poor Goldsmith!" How often we have heard this exclamation from the lips of those who loved his writings and bemoaned his struggles against the ever present menace of starvation? How freely also the privations of Francis Thompson have been exploited to enlist a sympathetic and possibly a commercial interest. Chatterton, too, De Quincy and others come to mind who, in early life, suffered hunger, misery and affliction.

But are these men entitled to such particular commiseration? Is there not, aside from the well nigh universal necessity of working to live, is there not in hunger itself, some measure of compensatory stimulation? In the very exigencies of poverty and distress, is there not a mysterious something that urges the soul onward to a more elaborate pursuit of its elusive visions?

Occasionally, too, we hear the remark that such and such a genius should be subsidized and much pity has been wasted on this irritable brotherhood because its members have not been maintained in luxury by some public or private benevolence. The idea springs from a misconception of the conditions under which such a mind will functionate, for the converse of our thesis should also be true, and we expect to set forth that a genius, surrounded by physical comfort, would be so buried under the shields of plenitude that his creative impulses would be stifled irrevocably.

Since the race is immortal, rather than any of its units, the progressive principle of mankind instinctively uses the individual as a means of promoting its mighty ends. In the working out of an all-embracing design, the stresses of life become stimulants which impel the spirit to seek its freedom in imaginative fields where compromise is unnecessary and fetters unknown.

Among the literateurs of the past, we find numerous instances, too numerous to be accidental, in which the work which brought renown was done during a period of hardship. It is highly probable, moreover,

that those productions would have been inferior, or even negligible, if the authors had lived in ease. At all events they would not have reached the rank of genius. "The air of the fireside," says Stevenson, "withers all the wildings of a husband's heart. He is so happy and comfortable that he begins to prefer happiness and comfort to everything else in the world, his wife included. Twenty years ago such a man was equally capable of heroism or crime. Now he is fit for neither. His soul is asleep."

If we regard this sentiment as the discontented growl of a bachelor or too much at variance with the metaphysical views we choose to entertain, yet we may incline to admit later that it is in fine accord with sincere psychologic doctrine. It is ultra materialistic, to be sure, but this is no embarrassment if the position be sound. We may not go so far as some of the older schools and attribute anger to the gall, joy to the spleen and love to the liver, but much is congenial in the theory of James and Lange that every emotion is the resultant of the organic impulses that converge to create it.

As far back as the seventeenth century, Descartes tried to show that a special set of organic operations prompted each of the six emotions he recognized as primary.

The psychology of that period was extremely primitive and the philosophers knew nothing whatever of glandular functions, but the prophetic hypothesis of Descartes has found excellent support among modern workers. Crile of Cleveland, Cannon of Harvard, Watson of Johns Hopkins and Angell of Chicago and others have shown that the pituitary, suprarenal, thyroid, thymus and similar structures are intimately confederated with the birth of the emotions.

The process works out quite simply. Let the gland or glands secrete more, or less, of their peculiar essence than usual, and the system at once shows the effect. Through deprivation, for instance, the cells in their glandular commonwealths are changed from complacent burghers to alert and excited warriors whose quickened functions rouse the faculties to a supreme efficiency. Tranquility is immediately transformed into conspicuous and dramatic movement. Fear, love, despair, joy, hope or ambition is produced and formally assumes control of the new activity. The individual is entirely at the mercy of such glandular impulses, for they are not to be restrained by wisdom or checked by morality.

Love is doubtless the most universally powerful of these glandular expressions, but it is reasonably certain that hunger, though merely a sensation, may easily rival the sexual instinct in the strength of its urge as it oft times exceeds it in bodily importance. Hunger and love are the two poles between which the world of humanity revolves. They are the primary functions of life. For the satisfaction of their imperious demands all vigor is acquired and all energy expended. In the attainment of these aims the brain weaves and works and sends shrewd inquisitors of thought in every auspicious direction. Chemical messages hurry to the brain from the viscera, emotions arise and mental orders for approprite action are sent out. It is need or desire that calls forth effort. A man neither craves nor dreams about the things he already has. Possession means calmness, a pleasure at rest, a desire satisfied.

Is a man starving? Visions of tables that groan under the weight of luscious viands will fill his mind by day and dominate his dreams at night. Is he thirsty? Fountains of crystal water will splash and tinkle for his expectant senses and the fateful mirage will loom before his feverish eyes. So the poet describes, not the things that are or have been, but rather the goals he burns most furiously to gain. The necessity of quenching innate personal passions, usually of glandular origin, inspires his song. When Mohammed wrote voluptuously about the black eyed houris of Paradise, he was still young and the blameless husband of an aged woman. Had he married a younger wife, the Koran would have suffered a marvelous change, for surfeit kills the imagination and satiety destroys art (Ellis). "If Matilda Wesendonk had eloped with Wagner in 1858, as he begged her to do," says Huneker, "Tristan and Isolde might never have been finished, or at all events, the third act would not have been what it is now."

Thus, while it is true that love is an intellectual and emotional stimulant of the first rank, yet it consistently obeys the law of satiety. In confirmation we may quote the case of de Fleury, whose patient, a well-known writer of great talent, confessed with truly French naïveté that whenever he experienced the ecstacy of love in the company of his mistress, he lost the power of composition for several days. Love has not been treated at length by either James or Lange, yet this emotion is really the best exemplar of their theory, for if, in a given instance, we suppress all the physiologic manifestations of the sexual

instinct, what have we left? Nothing. Not even the consciousness of a vague attraction.

The masterpieces of the world, all that is precious and best in sacred and profane literature, are the harvest of hungry souls, of souls ranging and questing but never satisfied. Yet they acquire their laurels only because they reproduce the intensity of the inspired authors at the time of their creation. This inspiration, whether spiritual or material is, to us, nothing but the symbol of the activating essence which arises in the cells and organs of the body. The product of a single gland, or an association of congenial influences, may engender an emotion, or it may happen that an excitement initiated by one organ will break the local barriers and involve other organs or glands, other functions or psychic states, through the medium of the sympathetic nervous system. When two or more glands or cravings act at the same time they may reinforce or neutralize each other, or the emotional field may become a confused tracery of induced currents, echoes and adumbrations through which utterance is difficult or impossible.

On the spiritual side, it is certain that most of the writings permanently bestowed in the world have been produced by visionaries of exceptional power, either mystic or otherwise. In these texts are many things which suggest a glandular confusion in conception or a lack of mental espionage in the exposition that is far from sufficient. Nevertheless, the obscurities and ambiguities are often accepted per se, as the signal evidences of a supernatural origin—the tenuous vestiges of a nebular creation. Do these works come from the clairvoyance of an alert and reasoning mind or are they dreams?

Dreams ordinarily originate in sleep, but there are waking hours wherein, under the intelligent control of the mental censor, a man transfers himself into artificial situations and reforms the world, or at least his relations thereto, according to his desires. After due residence in this fictitious edifice the artist seeks to give his dreams an outer and durable form. Lamb's "Dream Children" is a familiar and pertinent example. It is the wish fulfilment of Freud, but it is not subconscious, and it is far from infantile. Neither are these dreams sexual necessarily, though they may be, and often are, kindred to sex.

Not infrequently the tableau will be religious in type but strongly colored with sex, for "religion is the outgrowth of fear and love and so closely allied to sex," as Ribot says, "that this inexhaustible reser-

voir supplies or tinctures the major part of the protean religious manifestations. Each may, at appropriate times, reinforce, merge with or supplant the other." Religious exaltation is but a finer form of sex transport, and the visions of the seer pass up along the same electric filaments by which the visions of sexual ecstasy pass down. Spirituality is of necessity surcharged with sex for sexlessness is soullessness. The sex emotions however are joyous, sanguine and self-reliant, while the more dismal an emotion becomes the more truly is it religious. The solemnity of the Quaker, the melancholy of the Puritan and the depressive insanity of the early saints sufficiently illustrate the point.

All these manifestations, as well as their offshoots, direct and collateral, may arise, we repeat, from such states of consciousness as the physical conditions may create, either from within or without. An emotion of organic origin, or the sense of hunger, powerfully fixes the attention; the disturbing element is recognized and the faculties concentrate to quiet the clamor and bring about peace. The personality is cemented into a perfect mental and vegetative union which works energetically to satisfy a plangent need. Decision follows, and the end is attained with extraordinary facility.

The brain knows perfectly well that the body has a heart and a stomach, for every organ has a cerebral register, or what Carus calls a "psychic signature." The brain, however, is not merely the echo of internal sensations for it receives and reacts according to its disposition. "It centralizes indeed, but while taking its part in the concert, it puts its own mark on the impressions coming in" (Ribot). The brain may act as a center of exchange for the cells and transmit influences from one another, or it may happen that subtle intelligences will flow from one group of cells to others through directly communicating nerve filaments without cerebral intervention. Ultimately we may expect the exact tinge, merit and amount of impetus that each organ or function contributes to an emotion will be recognized and exactly differentiated, be it heart, kidney or stomach.

We may hope also that this disentanglement of the roots of the emotions will not only reveal psychologic states, but will permit us to interpret jealously the chemical and bacterial action taking place in the tissues and fluids of the body. Each emotion will then signalize some definite change which has markedly altered the quality of the

blood; a modification which, in turn, has brought about a specific reaction in the cells of the brain it nourishes. A contamination of the circulatory fluids inevitably perverts all organic and intellectual activity. The flora and fauna of the intestines, for instance, produce toxins that modify unmistakably the functional response of the various organs, especially the brain, to which the blood conducts them. Even more notable is the close alliance between the gastric secretions and pleasurable and painful states of the mind. Dyspeptics have a far from enviable reputation for being neither cheerful nor comfortable to live with. We cannot have strife and dissatisfaction in the stomach without a resultant unrest in the brain.

All physical agents that aid or diminish organic activity are capable ex officio of altering both nutrition and function. This we must admit and yet, says Ribot again, "feelings, emotions and passions have their primordial source in the organic, that is, in the vegetable activity. The states we know as needs, appetites, tendencies and desires are the direct result of every animal organization. They make up the true basis of emotional life." Even superficial reactions like heat and cold, sights and smells, bring about changes in secretion that beget emotions. These in turn produce mental pictures or visualizations. Every intense representation of an act tends to realize itself, for the vivid image is but the precursor of action.

The artist has representations that are exceptionally intense. He feels things violently. Ideas and associations are free flowing and pour forth abundantly from vital reservoirs. He dreams of orgies, love adventures, sanguinary dramas and virtues and vices of all kinds, but this imagery does not pass into physical action. The reason is obvious. The artist sees the incidents of his fancy, not as isolated units, but assembled and composite, and even as the sculptor sees a figure in stone so his brother wishes to perpetuate his dream in all its divine symmetry and perfectness. He objectivizes, therefore, by creating a work of art in which he lives and breathes and finds deliverance from a haunting idea. It is a period of exaltation in which the artist's design is executed with a maximum of energy and a minimum of consciousness. For the worker this is the best possible mood for production since the more intense the emotion becomes, the more attenuated is the intellectual element and, on the other hand, the clearer the perception, the weaker is the tone of feeling.

Thus far we have been concerned with the organic origin of the emotions and the method of their operation. The discussion is essential to our problem, but it is time to correlate these ideas and analogies with the subject of our thesis.

It may seem absurd to claim that an event so weakening as hunger could in any manner bring about results at all comparable to the soul-stirring effects of love, yet there is much testimony to its high value as an awakener of emotion.

We know that the consciousness of hunger is due to contractions of the muscles of the stomach, but whether this sensation acts as a direct excitant through glandular or cellular cravings or indirectly through the removal of intellectual control or breaks the envelop of generic inhibitions and thus releases ideas and subconscious states from the supervision of the censor, we have not learned. We are only entitled to report the clinical observation that in a condition of hunger the mind is so affected that associations, fantasies, dreams and inventions of rare quality flock across the threshold and pass from the penumbra into the light of day.

The physiologic facts of the process are described by Carlson of Chicago, who has studied the phenomenon exhaustively, not alone in the case of a peculiarly serviceable patient, but also more accurately in his own person. He informs us that while all the well-known gnawing sensations and pressure pains are present in the fasting individual, yet there is, in addition, a certain degree of excitability of the central nervous system. "The excitability is greatest when hunger is most acute. It is partly subconscious," he says, "and will depend upon the stability of the nervous system involved." This last statement is highly significant, as we have already shown. "Prolonged starvation," he continues, "appears at times to lead to heightened or abnormal cerebral activity as shown by the feeling of exaltation and by visual and auditory hallucinations. These phenomena are determined quite as much by the type of the emotional processes of the individual (intensity of interest?) as by the effects of starvation, since they are registered more frequently among religious ascetics than among the worldly minded."

Religious ascetics are usually extremely temperamental and therefore in this class, rather than among the "wordly minded," should the greater number of genuises be included. Their periods of inspiration

would doubtless equal in degree and possibly in frequency the transports of the ascetics in whom the elation that follows fasting is often confused with religious fervor. The ecstatics have abundantly recorded the principal features of their experiences under two heads: First, the restriction of consciousness to one overmastering center of association and second, the manifestation of rapture which is an emotional form of love, desire and pleasure of possession all combined. It is a focalization of consciousness accompanied by exaltation. In this happy state, the mind works with the greatest facility and the powers of expression are expanded wonderfully. It is another example of the cemented personality functioning in the highest degree of efficiency. The result, however, can never exceed the supreme possibilities of the individual

Carlson thinks the exaltation may be due to a depression of certain affiliated brain centers, which would correlate it with dreams, rather than to any actual increase in the excitability of the faculties. From another standpoint, it might be possible to explain the event as a temporary release from conventional inhibitions, or again, as a result of chemical changes in the blood induced by lack of nutrition. But whether it be a dream or an escape of the artist's true self from subliminal prisons or an impulsion due to altered metabolism is of minor importance, so long as the reality of the emotional upheaval is authenticated.

The after effects of Carlson's experience were also remarkable, and quite different from the tranquility, depression or even hebetude which follows the transports of love. "Both men," he says, "felt unusually well from the second day after breaking the fast." Carlson had the feeling that he had just returned from a holiday in the mountains. His mind was extremely clear and the amount of work accomplished, both mental and physical, exceeded the average. Thus, as frequently happens, the emotional wave persisted, or even increased, after the incitement had been withdrawn.

Carrington strongly corroborates Carlson. "In times of fasting," he testifies, "the senses are more alert, remarkably so and without exception. The eyes are bright and clear. Touch, smell and hearing are more acute, while taste becomes highly sensitized and more discriminating. The nervous system suffers least. Here, there is no loss of weight," for like sailors in times of stress who burn the woodwork

of the ship, the nerves feed on the less vital portions of the body. "Attention, memory and the power of association," he goes on to say, "are quickened and the ability to reason acquires an extraordinary brilliancy. Furthermore, there is an added appreciation of the more spiritual qualities like intuition, sympathy and love. The lack of nourishment energizes the will and clarifies the mind." Up to a certain point calculation and inductive reasoning is a matter of nutrition while emotion is not. When decision is due, the well nourished will deliberate and set forth his ideas logically. The underfed will emotionalize. When hunger is chronic or extreme, all the faculties are spurred to the utmost endeavor. It was not the mere absence of food that brought about the French Revolution, but through long deprivation came emotionalization with a resultant quickening of feeling and intellect. Moreover, as hunger pangs increase in pitch and persistence, the aggressive spirit becomes detached from larger loyalties and finds expression through personal and selfish channels. In this manner a vast outflow of emotion is generated by multiple organic cravings and accumulates until it is discharged by the catharsis of revolutions.

The full stomach, on the contrary, brings its own intellectual and social penalty. The assimilative acts take place in the inmost recesses of the tissues and organs. But what highways connect these processes with the cortex, that intensely vital layer on the surface of the brain? By what channels does the brain transmit its directive inquisitions or receive the echoes of the indolence, the haste, or the several modifications of the nutritive functions? Our information on this subject is not satisfactory, but it is clear that the business of nutrition depends especially on two elaborate systems of nerves, the great sympathetic and the pneumogastric, which are represented in some way in the outer layers of the brain.

Under the regulation of these nerves every particle of food must be worked up by the alimentary organs. It must undergo many complicated chemical changes, all of which demand energy from special structures and organs. When more food is taken in than growth and repair necessitate, there is a waste of force, a diversion of energy, and possibly so great a disturbance of the normal processes that systemic poisoning may occur. This poisoning may in turn reveal itself as a moral perversion or a mental irresponsibility. When all the organs

are functioning normally, the system is balanced and the brain works logically, according to the capacity of the individual.

Since only fifteen or sixteen ounces of proper food per day are necessary to support life, it is the rule to find overnutrition in civilized communities. Furthermore, anything that diverts the blood from an active organ interferes with or destroys that particular function. The brain, for instance, ceases to act when the blood is rushed to the aid of the struggling stomach—"that maid-of-all-work, battling against fearful odds." Digestion being accomplished finally, and at enormous expense, the transformed material is poured out into the system. In the overfed body the tissues are constantly choked, clogged or smothered by food products and fat is stored. Fat is waste, or excess, which has been deposited in the body instead of being eliminated. If through hunger we deprive the body for a certain time of its nutritional surplus, we give the eliminating organs a chance to unburden themselves and catch up. It is a true purification since the worthless matter is always first to go.

De Quincy, in his essay on Goldsmith, records an observation, derived possibly from his own experience, that "to be cloyed perpetually is a worse fate than to stand sometimes within the vestibule of starvation." Satiety means quiescence and stagnation. It is a discontinuance of spiritual evolution. Satiety curbs the questing soul. It restrains the normal desire of man to utilize all his faculties. With desire appeased, the imagination is either enfeebled or quenched, and the creative power of the mind is stifled.

We now come to an interesting phenomenon which is part of the dual endowment of man. Schopenhauer has remarked acutely, that "whatever direction we take in living our lives, there is always some element in our nature that remains unsatisfied and ever clamors for expression." This pent up passion may be released in some instances by representations of music or the drama, as Aristotle long ago suggested, but frequently, the inhibited aspiration demands a larger activity and the shackled soul-stuff struggles desperately for freedom.

This new path may be adventured in courses parallel or cognate with the one already traveled, like Gerome who, after a long and rarely successful career as a painter, laid aside the brush for the sculptor's chisel. More often, however, the issue of the feeling is antithetic to the individual's manner of life and apparently inconsistent.

The poet Yeats has noted and analyzed this curious occurrence and calls it the "development of the anti-self," which he explains as a "true self making its own experience." Mordell with the same idea names it "self-deception."

These bipolarized personalities are not infrequent among men of rich talent. Thus, we learn from Disraeli and Havelock Ellis that the most unchaste verse is often written by poets whose lives are blameless while, on the other hand, authors who have written most purely find their compensations in living impurely. Neurologists might call this a form of exhibitionism. Moore and Samuel Rogers are the examples Ellis chooses of the men who lived lives quite opposite to that of which they wrote, but such a list could be greatly enlarged. In fact, the licentious literature of the clergy might easily be an outlet rendered necessary by the austerity of their lives. In no other way could they escape the stiff-mindedness peculiar to chastity. Their unwonted repression inspires an over-emphasis on the nakedness of the flesh, while the conditions of their profession constrain them to a vicarious misbehavior. It is an old maid's insanity which, with Swift and Stearne at least, seemed to find physical as well as mental relief. Husymans remarks with his usual brilliant cynicism, that "much of this literature is so obscene that it could have been produced only by one who was chaste to asceticism." A more illuminating example may be found in the life of Corregio who, it is said, was timid, anxious, melancholy and penurious. He was always at work for his dependent family and yet he painted the Antiope, the Leda, the Io and the Paradise of Careless Joy in the nunnery at Parma.

If we may venture to alter a phrase of Yeats, we would say that Corregio's art was the compensating dream of a nature wearied by over-much renunciation. The word renunciation is the key to the problem of the conflict between life as it is and the starveling's dreams of what it should be. In life, we are forever giving up to circumstances, but in art, if it is worth while, the dreamer is inflexible. There is no mental or emotional renunciation but rather the fullest and most gratifying indulgence of personal expression. It is both a revolt and an ecstasy.

The artist achieves his ideals because they are the result of strenuous rebellion against the afflictions of his daily experience. In everyday life he longs insatiably for action as a mental and emotional outlet

for his ideas and his personality, but he receives only reaction, which is the physical response to a multitude of vexations, annoyances and denials. Thus it is the buried soul of man that strives for utterance, and its voice alone that finds immortality.

Corregio's true self, therefore, would be represented in the Paradise of the nunnery and in the search for passionate adventures among the nymphs of the forest. His nature, wearied by falsity to itself, threw off the masque and escaped, not from reality but into it. Such an escape is favored and actuated by physical demands like hunger and love, or by any other stress that leads the soul in desperation to break the chitinous inhibitions of caste and type and doff the livery of regimentation.

The greater the denial, the more vivid the dream; the fiercer the hunger, the clearer the vision. So we begin to understand how the gregarious Goldsmith, having failed to escape from himself by journeys about Europe, as described in the haunting lines of the "Traveler," came at length to believe neither happiness nor reality could exist for him except in the lowliest of villages and even that in process of abandonment. We begin also to appreciate how "a certain degree of abstinence is prerequisite to the formation of a breeding ground from which the dreams and images of desire may develop into the perfected visions of art."

But, you inquire, what is the connection between all this discussion and the subject of our thesis? Permit us to say, the connection is very close, for renunciation is repression and repression is—starvation. The habitual practice of chastity, sobriety, renunciation, poverty and hunger, leaves but one indulgence open to the artist and that is his dreams. "A mighty longing," contributes Huneker again, "is better for the birth of art than a world of facile happiness." But the longing need not be conscious. The feeling of existence is not found among the mass of men because with them it is continuous. When a man does not suffer, he does not normally think of himself, but let disease or privation appear with its attendant introspections, and he immediately discovers his ego.

Therefore, even if we do not meet with an engenderment, we may expect a liberation of artistry through hunger, a disengagement of the spirit from its inhibiting envelopes. To be sure, a temperament and a tendency must exist, for nothing of value can develop out of sterile

soil. We all know persons who have a gift for figures, music or painting which under proper conditions is capable of infinite expansion by exercise. In the same way any talent can be raised to the *nth* power through emotional strain or prolonged craving. We may cite, for example, the unhappy Keats who "was born with an unconquerable thirst for luxury," and we may rejoice to share in that sweet palliation of his disappointment and grief, which he drew from a glowing opulence of verse.

The case of Keats finds many repetitions among the devotees of the pen, and literature is regularly enriched by this apparent becripplement. Whether we consider the constant suffering of Pascal, which roused his emotions for the production of his famous "Meditations," or the misery of Thompson, which found escape in the "Hound of Heaven," or the gnawing hunger and despondency of Goldsmith, which gave us the lilt and lightness of the "Deserted Village," at all events, we cannot forget nor cease to be thankful for the literary artistry that comes when the brilliant but irresponsible faculties of genius have been focused and energized by disease or starvation. Without such stimulation Goldsmith might have been a simple curate in Westmeath rather than the famous author of "She Stoops to Conquer," and Thompson would have died without issue.

If humanity is advantaged, the individual must suffer. A genius is one who is doomed by his constitution and by his inalienable tendencies to bring forth his children in sorrow and alone, and throughout the years of whatsoever comfort he may secure, there will always remain on his flanks the scars of the parturitional lash.

The bluefish and the salmon, en route for the spawning ground, disregard all physical needs and make the journey fasting. Vocalists and athletes are well aware of the importance of an empty stomach when they wish to command their highest powers. The Hindoo, the Mongolian, the American Indian and the Jew, the ascetic of every tribe and generation has found in fasting an elevation of feeling so rapturous as to betoken a communion with Deity, and what matter if the hallucinations and visions that close his trial are sincerely accepted as tidings from the Most High? The stimulation is incontestible and the human soul is raised to new levels of perception. Elijah and Moses passed forty days without food, and the Redeemer himself

sought through fasting to bring his soul into free and unrestricted filiation with supreme spirituality. So also the painter, the philosopher or the poet may well purge his gross body of its impurities, being thereby assured that his mind will receive a myriad of new associations and contrasts. His imagination will be stimulated to higher and broader flights; he will be enabled to sublimate his tyrannous appetites; he will divert his corporeal excitation into emotional fields and produce an artistry which is at once a joy to the world and a bid for immortality.

The reveries and the waking dreams of man are normally the antithesis of his social perturbation. Goldsmith was a "child of the flesh," who yearned for a sequestered spot unconscious that he could not live therein. This was his affliction and also his redemption. The surface irritants were indispensable to the flowering of his genius. He existed in a world full of heartaches and antagonisms to which his emotions constantly reacted while his mind, with equal insistence, sought its own form of action—the desire being intensified by prolonged refusal. His art was the compensating dream of a life wearied by overmuch renunciation. In the "Deserted Village," the "Vicar of Wakefield," the "Traveller" and "She Stoops to Conquer," he sought an escape into reality from the restraints of circumstance. "He walked in no high altitude," as De Quincy says, "but at an elevation easily reached by the ground winds of calamity. From that cup of sorrow which is pressed upon all lips in some proportion, he was compelled to drink through the very tenure by which he held his gift," yet always with advantage to his accomplishment. But even so, are there not exceptions? Yes, for some there are whose powers transcend our human limitations but "it is only these Children of Paradise, the Miltons of our planet, who have the privilege of stars—thus to dwell apart." It is in solitude on his own particular pinnacle that the genius fasts and dreams his dreams. He is surrounded by spirits and assailed by demons. He hears the beating of their wings as they troop past. A lordlier form of terror hovers near, but grim and undismayed the prophet consecrates his powers to the purpose preordained. Withdrawn and silent, he broods over his destiny until his time is accomplished, then the shining vision springs into being, the deathless dream that stirs the souls of men to nobler aspirations and to deeds of high emprise. It is a vibrant call which restores the fainting heart and

forever renews the longing for endeavor on fresh planes by its mysterious and opportune purveyance.

But what of the human parent of this puissant offspring? Nothing. He has endured the swift mutations of joy and pain and elected his reward. His work is done. He seeks not, nor obtains, wordly sympathy. He has tasted divine ambrosia, and, feeling his quick relationship to celestial comrades, he would not change his one short day of royal ecstasy for the perdurable years of any man.

STANTON ABELES FRIEDBERG

1875-1920

Stanton Abeles Friedberg died May 27, 1920, as a result of complications from an attack of acute otitis media.

Dr. Friedberg was born in Chicago, Dec. 1, 1875. He received his preliminary education in the public schools of Leavenworth, Kansas, attending University of Michigan one year. He entered Rush Medical College in the fall of 1893 and graduated in 1897. He served one year's internship in the German Hospital of Chicago, and, after practicing general medicine for three years, he became assistant to the late Dr. E. Fletcher Ingals, beginning his lifework in the practice of otolaryngology. In 1905, he was made assistant in the department of laryngology at Rush Medical College, and in 1913 became assistant professor. He became a member of the staff of Cook County Hospital in 1906, and was made chief of the department of otolaryngology in 1913, holding this position until the autumn of 1919. He was made assistant to the attending laryngologist at the Presbyterian Hospital in 1909, and later became attending laryngologist.

Dr. Friedberg was justly proud of his service during the World War. In November, 1917, he was commissioned Major, M. C., and served eight months at the Base Hospital at Fort Sill, Oklahoma. At the end of this time he was sent to France with Base Hospital No. 85, serving eight months with the A. E. F., and was discharged May 1, 1919.

Dr. Friedberg was a member of the American College of Surgeons, the American Laryngological Association, the American Laryngological, Rhinological and Otological Society, and the American Peroral Endoscopists. He was also a member of the American Medical Association, the Chicago Medical Society, the Chicago Laryngological and Otological Society, as well as the American Academy of Ophthalmology and Otolaryngology.

His most noteworthy contribution to scientific medicine was work carried out while he occupied the position of consulting otolaryngologist at the Durand Hospital of the John McCormick Institute for Infectious Diseases. This work was in connection with diphtheria carriers, and he established the signal value of tonsillectomy in such cases. Since the death of his teacher, Dr. E. Fletcher Ingals, Dr.

STANTON A. FRIEDBERG

1875-1920

Friedberg has been recognized as the most capable operator in the field of bronchoscopy in this part of the country. He early acquired an interest in the history of medicine and wrote a number of papers on the history of his specialty. He acquired an unusual library of historical texts, engravings and reference books relating to otolaryngology.

He was married to Aline Liebman of Shreveport, La., in 1906, who survives him. He also leaves three children, Stanton, Jr., Jean, and Louise.

In Dr. Friedberg were combined the highest professional skill, a sense of integrity and fair dealing, and a genial personality which endeared him to his professional associates as well as to his patients. In his death the Institute loses one of its ablest members.

JOHN EDWIN RHODES
GEO. E. SHAMBAUGH

REPORT TO GOVERNORS OF THE INSTITUTE OF MEDICINE OF CHICAGO OF A COMMITTEE APPOINTED TO INQUIRE INTO THE QUESTION OF NECROPSIES IN THE HOSPITALS OF CHICAGO

A questionnaire and explanatory letter were sent to fifty-one hospitals in Chicago having 50 or more beds. Replies were received from 36 hospitals that have a combined bed capacity of 7,304. The fifteen hospitals from which no report was obtained have a reported bed capacity of 2,376. The figures in this report therefore cover about three fourths of the bed capacity of Chicago hospitals of 50 beds or more.

In the 36 reporting hospitals having 7,304 beds, there were 142,990 admissions in 1919, and 7,934 deaths. Permission necropsies were made in 789 cases and coroner's necropsies in 251 others. The later figure does not include coroner's necropsies at Cook County morgue. Omitting Cook County Hospital, 35 reporting hospitals had 4,405 deaths in which permission necropsies were made in 474 cases. Deducting coroner's cases, permission necropsies were obtained in slightly over 11 per cent. of cases.

The percentage of permission necropsies varied widely. Six hospitals reported over 20 per cent. of permission necropsies, 4 hospitals 10 to 20 per cent., 14 hospitals 1 to 10 per cent., 7 hospitals no necropsies, and 4 made indefinite or no statements as to necropsies. In one hospital with a percentage of 48.4, there were performed 30 per cent. of the entire number of 474 necropsies, and in the 6 hospitals reporting percentages of over 20, 56 per cent. of all the necropsies were made. Seven hospitals report that no permission necropsies were made; in these hospitals there were 91 coroner's necropsies out of a total of 251 for the 35 reporting hospitals.

All 35 hospitals report that they have rooms for the examination of the dead, of which 25 are regarded as adequate, 7 as fair and 3 as inadequate. Twenty-five of the hospitals have pathologists, of whom 15 are reported as full time, and 10 as part time. In 7 hospitals there is no pathologist, and examinations are made by a technician in 4, by

intern in 1, and no provision in 2. In one of these hospitals, which is noted for its surgical work, there were 217 deaths and 8 necropsies.

The attitude of the hospital administration toward necropsies is reported as favorable in 32, and one reports that there is no objection to necropsies. The attitude of the staff is reported as favorable in 29, indifferent in 4 and lax and careless in 1.

Before discussing reasons for the small numbers of necropsies, and the remedies therefor, it is desirable to note the difficulties reported by the hospitals themselves. In the order of frequency in which they were reported, the difficulties encountered in getting necropsies as given in the reports were: (1) religious scruples, (2) opposition of undertakers, (3) prejudice, (4) fear of mutilation of bodies, (5) lack of organized effort by the staff, (6) lack of contact between physician and relatives. One hospital, in which there were but 4 necropsies in 56 deaths, stated that no difficulties were encountered, a situation perhaps more hopeless than in most of the others.

Certain undertakers regularly stand in the way of necropsies; others are better informed, and cooperate with physicians in advancing medical science. The opposition of undertakers usually takes the form of an appeal to the ignorance of relatives and friends as to what is contemplated in a necropsy, and is effective frequently because the physician has failed to deserve and establish a close relation with the family.

There is something to be said for the undertaker, who has frequently found vessels essential to proper embalming unnecessarily damaged by the pathologist. Frequently, too, there is unnecessary delay in the signing of death certificates, and undertakers are required to wait at hospitals for from 2 to 4 hours for a signature which could have been obtained more promptly. This enforced waste of time adds to the irritation of undertakers, and tends to increase opposition.

While religious scruples present a serious obstacle to the obtaining of permission for necropsies, especially in some hospitals, and while prejudice and ignorance are often unsurmountable, the chief reason for the small number of necropsies in hospitals lies, however, in the indifference of the staff, whether admitted or not, and the lack of organized effort to improve the standard of diagnosis of the hospital. Failure to make an earnest effort to obtain a necropsy is often the natural sequence of failure to insist on good history, physical examination, laboratory examinations and progress notes. Continued neglect

NECROPSIES IN CHICAGO HOSPITALS IN 1919

Name of Hospital	Beds	Patients	Deaths	Necropsies		Per centage of Permission Necropsies	Part or Full Time Pathologist	Medical School Affiliation	Name of Pathologist
				Permission	Coroner's				
American	125	4,000	74	9	3	12.1	Full	None	M. C. Wells
Alexian Brothers	280	3,360	304	15	25	4.9	Full	None	Bro. Surgius
Augustana	200	4,190	217	8	6	3.7	None	None	
Chicago Fresh Air	104	307	89	Few	...	....	None	Northw.	
Chicago Lying-In	120	4,350	38	3	0	8.0	Part	Yes	
Children's Memorial	175	2,391	203	47	2	23.1	Full	Rush	R. S. Austin
Cook County	2,000?	27,819	3,529	315	?	8.9	.....	.....	Fred Stangl
Durand	60	733	41	10	0	24.4	Full	Rush	L. Hektoen
Garfield Park	60	1,462	60	0	0	0.0	Full	None	Josef Sielin
German Deaconess	60	2,654	96	2	14	2.0	.....	None	W. H. Buhlig
Hahnemann	130	2,983	118	30	1	25.4	Full	Hahne.	W. H. Wilson
Home for Destitute and Crippled Children	115	1,096	7	0	0	0.0	.....	Rush	
Illinois Central	110	2,305	92	3	0	3.2	Part	None	Mary H. Swan
Isolation	35	306	0	...	...	....	None	None	
Lakeside	85	2,006	90	0	10	0.0	Full	None	Herman Boettcher
Mary Thompson	75	1,861	56	4	1	7.1	.....	None	
Mercy	354	5,813	191	25	6?	13.0	Part	.....	
Michael Reese	440	9,123	368	33	?	9.0	Full	None	O. S. Schultz
North Chicago	90	1,935	46	Few	0	....	Full	.....	Hirshberg
Norwegian-American	125	3,176	161	0	0	0.0	None	None	Technician
Park Avenue	64	450	40	0	12	0.0	.....	None	Intern
Passavant	75	2,301	75	0	30	0.0	Part	None	Alvin Thompson
Peoples	40	1,030	57	0	22	0.0	None	Northw.	
Presbyterian	425	9,908	297	144	14	48.4	Full	Rush	B. F. Raulston
Ravenswood	50	1,425	44	6	4	13.6	.....	None	J. J. Moore
St. Anne's	100	2,717	139	3	24	2.1	Part	Loyola	Geo. W. Wilson
St. Anthony	176	3,623	209	10	32 (inquest)	4.7	.....	None	Fred Olentine
St. Bernard's	200	5,201	255	4	20	1.5	Part	None	J. J. Moore
St. Joseph's	166	4,224	149	32	10	21.4	Part	Rush	W. M. Burmeister
St. Luke's	400	9,527	295	52	?	17.6	None	None	E. F. Hirsch
U. S. Marine	130	1,036	28	6	2	21.4	.....	.....	Miss Eleanor Murray, Tech.
Washington Boulevard	85	2,395	61	5	12	8.2	.....	None	C. E. Watts
Washington Park	110	4,000	93	3	5	3.2	.....	None	De O'Connor
Wesley	275	6,681	251	20	15	7.9	Full	Northw.	F. R. Zeit
West Side	155	4,146	111	0	18	0.0	Full except 2½ days a week	None	L. R. French
Willard	110	2,756	60	0	4	0.0	Full and part	Loyola	B. H. Orndoff

of necropsies contributes to subsequent failures in diagnosis and in rational treatment. The postmortem examination confirms or disproves the clinical diagnosis and gives additional information of value to the clinician in subsequent practice, and the interest of the staff of a hospital in necropsies is one important index of its efficiency in treating disease and of the grade of work done in the hospital.

It is the belief of this committee that the alleged prejudice against necropsies is not so great as has been assumed, and that it is advanced as an excuse when the real reason is indifference on the part of the staff, including the pathologist.

In one large hospital in which there are a number of coordinate medical and surgical services, with approximately the same material and number of deaths, the number of necropsies varies directly with the interest manifested by the attending physician or surgeon and as a direct result of association, by their interns.

The physician who gives his patients and their relatives careful individual attention will in the event of a fatal outcome be accorded a much more kindly reception when he requests a necropsy than will the physician who has treated his patients by routine as so many cases. Devoted effort to save life makes the strongest appeal to relatives when a postmortem examination is requested.

RECOMMENDATIONS

The following recommendations are submitted:

1. That in view of the great importance of necropsies in improving the standards of medical practice, the INSTITUTE OF MEDICINE take such steps as appear wise to assist hospitals to increase the number of necropsies. Discussion in hospital staff meetings of the subject of necropsies, the posting in a suitable place in the hospital of tabulations of the percentage of deaths in which necropsies were obtained, the elimination of unnecessary delay in the signing of death certificates for undertakers, the establishment of adequate laboratory facilities with a pathologist in active attendance at the hospital, closer cooperation between the pathologist and the physicians and surgeons on the staff, and above all, the encouraging of a more active personal interest in patients by the attending physicians and surgeons, whereby they will come in closer contact with the friends and relatives of patients, to the advantage of the patient, hospital and doctor alike, are among the ways

in which the number of necropsies may be increased, and the standards of hospital medical practice improved.

2. It is believed that the neglect of necropsies is largely a matter of inertia and failure to realize their value rather than of intent on the part of the staffs, and it is therefore recommended that this question be called to the attention of each hospital staff.

3. It is recommended that a further survey of necropsies in Chicago hospitals be made next year.

ERNEST E. IRONS, Chairman
D. J. DAVIS
J. P. SIMONDS
A. FRICK
ALLAN KANAVEL

ANNOUNCEMENTS

The Board of Governors has accepted an offer from a source that at present cannot be revealed, of $250.00 annually for a lectureship to be known as the Pasteur Lectureship of the Institute of Medicine of Chicago. The first Pasteur Lecture is published in this issue.

At the beginning of 1920 there were 215 active Fellows of the Institute. During the year 2 resignations, 2 deaths and the transfer of 3 Fellows to the nonresident roll caused a loss of 7, which, however, was offset by a gain of 29 new Fellows, leaving a total membership of active Fellows of 237.

The Treasurer's report for 1920 shows receipts of $9,427.96, and expenses $1,403.19. It is the policy to invest all accumulated funds in bonds and other securities, and at present the investments total $38,000.00.

New Fellows, if they wish, may obtain all back numbers of the Proceedings by notifying the Secretary.

The following were elected Fellows of the Institute since Jan. 1, 1920:

Channing W. Barrett
Albert M. Moody
Richard S. Austin
Edward H. Hatton
John Foote Norton
Douglas Singer
George H. Coleman
Frederick W. Gaarde
Walter H. Theobald
Robert Blue
Nathan S. Davis, III
L. C. Gatewood
James R. Greer
Selim W. McArthur
Harold E. Jones
Fred M. Smith
Alice Hamilton
Ruth Tunnicliff
Don P. Abbott
Robert J. Gay
William H. Burmeister
Robert P. Black
Frank W. Blatchford
Eugene Cary
John Favill
Hugh N. MacKechnie
Walter H. Nadler
L. J. Osgood
M. L. Goodkind

At the annual meeting of the Institute, Dec. 7, 1920, A. I. Kendall (to fill vacancy), D. J. Davis, S. J. Walker, and J. Gordon Wilson were elected governors.

At the annual meeting of the board of governors George H. Simmons was elected president of the Institute for 1921, and C. Judson Herrick, vice president. L. Hektoen was elected chairman of the board of governors, J. A. Capps, treasurer, and Ernest E. Irons, secretary.

THE SENSITIVITY OF NORMAL AND DEFECTIVE EARS FOR TONES AT VARIOUS FREQUENCIES

JOHN P. MINTON AND J. GORDON WILSON

January 25, 1921

The anatomic structure and the physiologic action of the ear have proved most difficult to investigate. In the eye, with the ophthalmoscope, one can see into and through the conducting media to the endings of the nerve. It is otherwise in the ear. In the normal ear the drum membrane shuts off the tympanic cavity from observation; with this membrane gone we get a view of the cavity, usually distorted. Under no circumstances can one see the nerve ending in the living. To make examination more difficult, nature has enclosed this nerve ending in extremely hard bone. If one desires to investigate the ending, after removal of the bone from the skull, the dense bone must either be broken or decalcified. If we break the bone, tearing of the soft structures results; if we decalcify, the decalcification with its acids and alcohols inevitably leads to changes in the delicate structure. In spite of these difficulties, we have a fairly accurate anatomic knowledge of the ear, sufficiently clear to indicate that here we have the most complex peripheral end organ with which nature has endowed man. This complexity, together with the analysis of sound it is capable of effecting, has offered a tempting field for speculation as to its mode of action. Yet little has been done in actual physical investigation of the living organ itself.

Within the last decade we have learned to apply to clinical cases, that physiologic knowledge of the vestibular function of the ear which had been growing up for half a century before this time, and as a result we have advanced the diagnosis of peripheral vestibular lesions and thrown some light on obscure central lesions involving the pathway and connections of the vestibular nerve. But in the field of hearing our physiologic knowledge and our clinical application of it are much as Helmholtz left it 50 years ago.

All agree that the ear is a mechanism constructed for at least two purposes: (1) to conduct sound vibration; (2) to perceive simple harmonic waves (simple tones), and to resolve into their component parts (simple harmonic waves) aerial vibrations compounded of different frequencies (pitches) which reach the ear together, and in this

analysis to stimulate nerves spread out in a particular linear formation. To what degree this analysis takes place centrally or peripherally does not concern us at present.

There are few subdivisions of medicine in which the specialist is more indebted to and dependent on the physicist than in otology. The middle ear which serves to conduct the sound waves, is designed, as Helmholtz pointed out, to solve the mechanical problem how best to transform a motion of great amplitude and little force such as impinges on the drum, into a motion of small amplitude and great force, such as has to be communicated by the stapes to the fluid in the labyrinth. The second part of the problem, which refers to the means by which the nerve endings are stimulated and the transformation of simple or compound sound vibrations into nerve vibrations, is no less a physical problem, for the internal ear contains at least three structures apparently capable of being set in vibration by sound waves.

In investigating hearing much has been attempted in the past by taking known anatomic structures and endeavoring to endow them with requisite physical properties. In pursuance of this, mechanical models have been built incorporating known anatomic data to show how the ear functions. The results have been stimulating but not satisfying. The attempt is here made to reverse this point of view, namely, to get physical data about audition in normal and defective ears and later to apply these to the normal or pathologic conditions present in the ear examined. The hope is that by a study of such cases we may arrive at a clearer knowledge of the physiologic functions of the various factors which enter into the peripheral mechanism of hearing.

The classical work on hearing was written by a physicist and physiologist—Helmholtz. In 1862, he published his "Sensations of Tone" and propounded his resonant theory of hearing—a theory modified by himself in later editions as new anatomic data were added, a theory which in spite of many objections still influences the work of physiologists and in which the central idea of analysis of sound by resonance has the support of most of them. From the stimulus of that work most of our great aurists of the past drew their inspiration, and on its results they explained many of their clinical findings. That work, Helmholtz tells us, necessitated new instruments of research. We have in the audion oscillator an instrument which far surpasses in its accuracy and delicacy any of its predecessors, and we have tried to harness it to the work.

To test hearing we have methods which enable us to ascertain fairly accurately whether the lesion lies in the conducting mechanism of the middle ear or in the nerve including its endings. This is a wide generalization which has served well in the past, but which leaves much that is important unanswered. Thus, we have no test allowing us to state where in the conducting mechanism the fault lies. Supposing the drum membrane should be indrawn and have its curvature altered, we are not able to say whether the deficiency in hearing is due to this or to some added deficiency of movement of one or more of the ossicles; or if the membrane should be relaxed, we are unable to state how much deficiency of hearing hereby results. Various questions are constantly presenting themselves, to which we can give no satisfactory reply; such as which defaults in hearing are associated with perforations in various quadrants of the drum—quantitatively and qualitatively, or, in combinations of middle ear and nerve deafness, which factor predominates and to what degree. During war service at the front one of us (J. G. W.) noted cases of deficiency of hearing corresponding to what the ophthalmologist calls limitations of the fields of vision—a marked diminution of hearing in which there was absolute deafness at both ends of the scale, the remaining zone of hearing much diminished in acuity corresponding to regions of recognized maximum sensitivity, a condition which might be regarded as due to a general depression of hearing. Until now we have had no method of mapping these out with any degree of accuracy. Then there is the question of "choked labyrinth," corresponding to choked disk, the importance of which need not be elaborated.

It has long been recognized by physicists that the estimation of the minimum audibility of sound at all pitches is of prime importance in the study of audition. But the range of tones to be examined and the difficulty of obtaining suitable apparatus capable of examining such audibility over so great a range have proved a great barrier. Various methods have been used to estimate the minimum intensity of sound at a given pitch necessary for audibility (the amplitude of just audible sounds). Thus Rayleigh for high notes used a whistle operated by constant air pressure, and tuning forks for low notes.* The whistle was mounted on a Wolfe bottle, attached to which was a siphon manometer to regulate a constant air pressure. The distance at which the sound could be heard was ascertained under as far as possible constant atmospheric conditions. One serious objection to these observations was

the distance the observer had to go from the source of the sound—in this case 820 meters—involving the disturbing influence of atmospheric factors. To estimate the minimum audibility of low notes, tuning forks were used which enabled Rayleigh to approximate the sound to the ear. Most of the physical observations of audible sounds and some of our best clinical testings have been made by the use of tuning forks used in various ways. Thus, to test the minimum audibility Gradenigo, an Italian otologist, attached to the upper end of a fork a dark triangle on a white background. When the fork is struck there is a double vision. One sees two pale triangles with a black triangle common to both; the greater the amplitude the greater the space separating the two triangles; as the amplitude diminishes the two triangles merge more and more into the single black triangle. By noticing the extent of the field when the patient ceases to hear (marked by a millimeter scale), one can estimate the hearing power. This method, however, is only applicable to low tones.

The siren, one of the oldest instruments to produce a continuous series of sounds at different pitches, has frequently been used to estimate the minimum audibility of sound. Wien, whose work is quoted freely by German otologists and physicists, used an electric siren conveying the sound to the ear by means of a telephone. He placed the maximum sensitivity of the ear to sound at about 1,200 to 2,000 d. v., from which area the sensitivity dropped off rapidly on both sides. His results, which have been extensively quoted by physiologists and otologists, do not appear to be generally accepted by physicists.[1]

Recently at the State University of Iowa, in the otologic and psychologic department, a modification of the electric siren (an audiometer) has been used to estimate the minimum audibility in normal and defective ears. The curves outlined are defective in so far that the instrument has failed to give the minimum audibility at pitches between 1,000 and 2,500 d. v.[2] Further, no corrections seem to have been made for the vibratory characteristics of the receiver, and with a given strength of current the absolute intensity of sound has not been determined. It is also difficult to see how overtones can be excluded by this instrument. Yet with all these defects, for comparative results it is claimed the instrument has proved valuable for otologic work.

1. Winkelmann: Handbuch der physik., 2, p. 248.
2. Trans. Amer. Otol. Soc., 1920, 15, p. 37.

Not only is the estimation of the minimum audibility of sound at all pitches important for the understanding of audition, but the testing of minimum audibility of various pitches is of importance in otology: (1) To determine the degree of impairment of hearing; (2) to localize the pathologic changes, for ocular examinations may give a negative result in deficiency in hearing, and (3) to estimate the results of our treatment.

The difficulties encountered in testing hearing are considerable. In testing sight we have white light. In testing the ear we have in nature no uniform sound to use as a standard. Both light and sound are vibrations, but the eye is not able and is not called on to resolve light into its composite colors, and even if it were the range of such vibrations is small compared with the ear. In the ear we have a special differentiation of function for such analysis of range.

In estimating hearing, we must have an estimate of the range of hearing (quality of hearing) and the quantitative degree at each pitch. Only with such a record can one have an accurate knowledge of the degree of hearing a patient possesses. Hearing for one part of the scale may be seriously impaired while that of another part is hardly affected. Accurate results can be obtained by estimating quantitatively the hearing for simple tones at all pitches. When one remembers that the qualitative range may be estimated at from 20 d.v. to 20,000 d.v. or higher, one recognizes the wide area to be covered.

At present we depend almost entirely on tuning forks. The overtones in the lower forks are got rid of by clamps and in the higher forks are so much higher that they do not interfere with our present application of the test; we are also aided by the fact that the fundamental tone persists longer than the overtones. Tuning forks, however, have great limitations. They are wanting in scientific accuracy because we cannot well measure the amplitude of their vibration. Each vibration period varies in each set and alters with use. It has been impossible to give a percentage estimate of the impairment of hearing in one ear compared with normal by means of forks, for the amplitude of the tuning fork when it ceases to be heard in the two ears is difficult to estimate.

We have at present no satisfactory means of measuring the intensity of the sound perceived. There is no certainty in regard to the position in the sound scale in which the maximum sensitivity for sound perception lies. Only by observation, such as will be outlined, can we get any such knowledge.

The audion oscillator helps to solve a number of these problems. As will be pointed out, it has shown how similar the curves are in some of our more defined ear lesions. It has shown how a defective mechanical conducting system affects, not a part, but the whole range of hearing. It shows in a surprising way how nerve lesions may differ from lesions in the conducting mechanism—a fact which appears to us to be of fundamental importance in the interpretation of the function of the cochlea. It has thrown interesting light on that most common but most elusive of sensory phenomenon—tinnitus. Above all, the graphic representation of the tone perception in defective ears compared with normal ears affords a startling picture of the degree of loss of hearing.

The accuracy with which the minimum amplitude can be measured is exemplified by testing the same person weeks apart with a minimum of discrepancy, an average deviation of not more than 5 per cent. The application of the oscillator to this problem has not been unattended with difficulty; for instance, the ordinary telephone receiver must be discarded and one constructed of a known natural vibrational frequency—a natural vibrational frequency higher than the pitches we are dealing with. This enables one to get rid of an error which has marred previous published results.

The cases observed by us may be divided into two groups:

1. Those patients who from our present knowledge may be classed as normal, that is, whose ears are positive to our tests for hearing.

2. Those who show deficiency in the hearing tests, including those with and without observable pathologic lesions.

The data presented are limited to an estimation of the minimum audibility of sound at various pitches over a definite part of the auditory scale, from 100 to 5,000 d.v., in normal and diseased ears. We have restricted observation to these ranges because these are the areas most useful to man; they include pitches usually tested and are of sufficient range to detect defects in the conducting and defects in the nerve mechanism as we at present view them.

The question has been raised whether bone conduction interferes with results, for instance, in such a disease as otosclerosis. We have experimental evidence sufficient to answer this in the negative.

In this presentation no attempt will be made to enter debatable territory. We attempt only to state facts as observed by the clinician and facts as obtained by the physicist. It is hoped that by an accumulation of such data trustworthy deductions may be drawn.

METHOD OF TEST

The audion oscillator has been adapted to the purposes of these tests. This oscillator produces a pure sine wave electric current whose frequency or pitch may be varied from 100 to 5,000 or more double vibrations per second. This current is passed through a current adjusting resistance, then through an electric filtering device which takes out any harmonics that might exist, and then through a suitable resistance network into which a special telephone receiver is connected. This receiver is the one used for determining the minimum audibility current at various frequencies for the person who is being tested. A suitable switch is provided to enable the person to listen for intervals of a few seconds, with the tone off between. This insures the reaching of the threshold of audition and completely avoids any fatigue that otherwise might arise.

The results of these tests may be graphically shown in two ways. First, we may plot as a function of frequency the ratio of the current for minimum audibility for an average normal ear to the minimum audibility current for ears being tested, whether they are defective or normal. This gives a graphical picture at all frequencies of the degree of hearing possessed by the patient as compared with the normal ear chosen for reference. Second, we may plot the sensitivity of the ear at various frequencies, when we mean by sensitivity the reciprocal of the minimum vibrational energy for audibility of the special telephone receiver diaphragm at the various frequencies. Both of these methods involve considerable calculations and an accurate knowledge of the characteristics of the telephone receiver. For an understanding and interpretation of the curves it is not necessary to give these details, and they will be omitted for the present.

TESTS OF NORMAL EARS

A number of normal ears, that is, ears without any known physiologic defects, have been tested. Sensitivity curves for two of these ears are shown in Figures 1 and 2. The ordinates of these curves are the reciprocal of the vibrational energy in ergs of the special telephone receiver diaphragm for minimum audibility. The frequency in double vibrations per second is plotted as abcissa. Figure 1 is the curve of a person about 35 years old while Figure 2 is that of a person about 20 years old. The degree of hearing of the former is quite inferior to that of the latter, especially for frequencies above 800

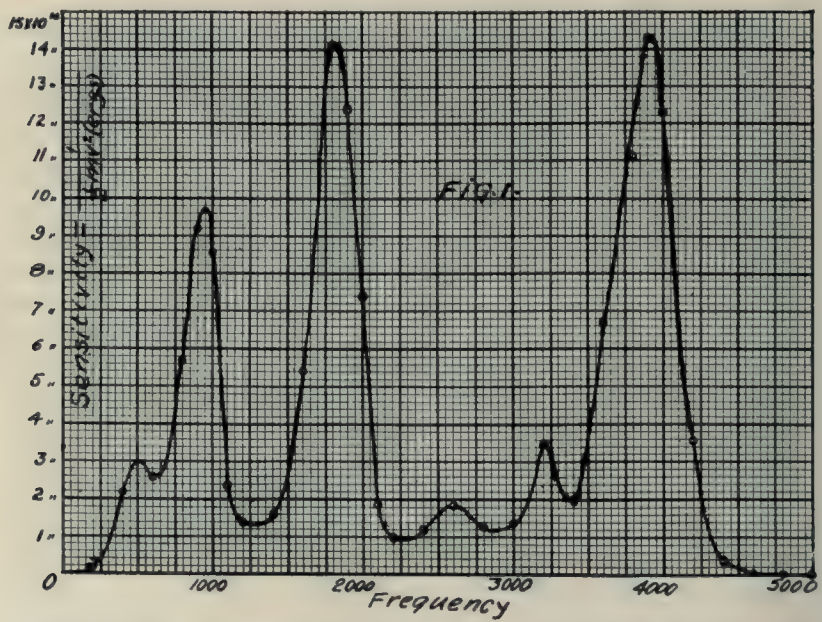

Chart 1.—Sensitivity curve for normal ear of a person 35 years old.

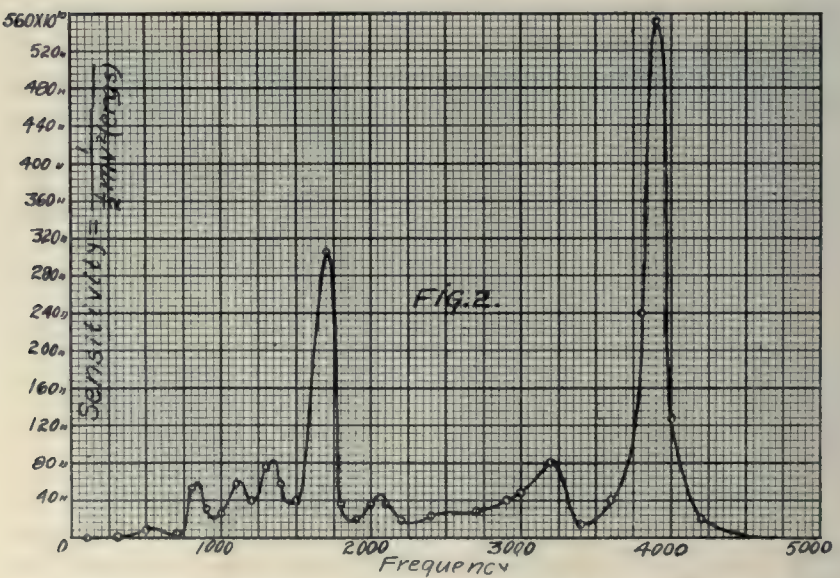

Chart 2.—Sensitivity curve for normal ear of a person 20 years old.

double vibrations. When comparing these two curves, however, one should bear in mind that these curves are in terms of vibrational energy of the special receiver diaphragm whose natural period was 5,215 double vibrations per second. The curves are not in terms of sound intensity or in the degree of loudness as perceived by the ear. Data to be published later will contain these two aspects of hearing.

The most important and interesting things shown by these curves are the large variation in sensitivity at the different frequencies and the existence of such definite maxima of sensitivity. The maxima in the region of 1,800 and 3,900 d.v. are practically in the same location for both ears. These peaks cannot possibly be due to the receiver for its resonant frequency was 5,215 d.v. Moreover, the peaks occurred in practically the same location when the tests were made with the natural period of the receiver in the region of 3,700 d.v. The peaks also occurred in the same region when the cavity formed by the receiver and the auditory canal was almost completely eliminated. Hence, these maxima are not due to the receiver or to the air cavity referred to. Tests with two different oscillators also gave the same maxima. We feel justified, therefore, in drawing the conclusion that these maxima are due to the vibratory characteristics of the mechanical parts of the ear considered as a complex vibratory system.

The well defined maximum at 900 d.v. for Figure 1 is absent for Figure 2. Nevertheless, both curves agree in that the sensitivity begins to increase rather rapidly near 700 d.v. and reaches a peak between 800 and 1,000 d.v. It is also of considerable interest to note that in Figure 1 the peak at 1,800 d.v. is double the frequency of the first maximum and that the peak at 3,900 d.v. is about double the frequency of the one at 1,800 d.v. In a complex coupled mechanical system, which the human ear resembles in many respects, the maxima are not to be thought of as harmonics of the first maximum, but rather as resonant frequencies of the particular coupled system.

Curves are being taken of more normal ears, and when a large number of them have been tested we shall be able to place more reliance on the conclusions than we are able to at the present time.

TESTS OF DEFECTIVE EARS

Tests have been made of numerous ears with various pathologic defects, but the results of these tests will be given for only a few cases.

A more detailed account of the present work from the physical point of view will appear in a later paper to be published in one of the physical journals.

Figures 3, 4, 5 and 6 contain curves for certain types of deafness. These curves show a graphical picture of the relative receiver currents for minimum audibility at various frequencies. If these relative

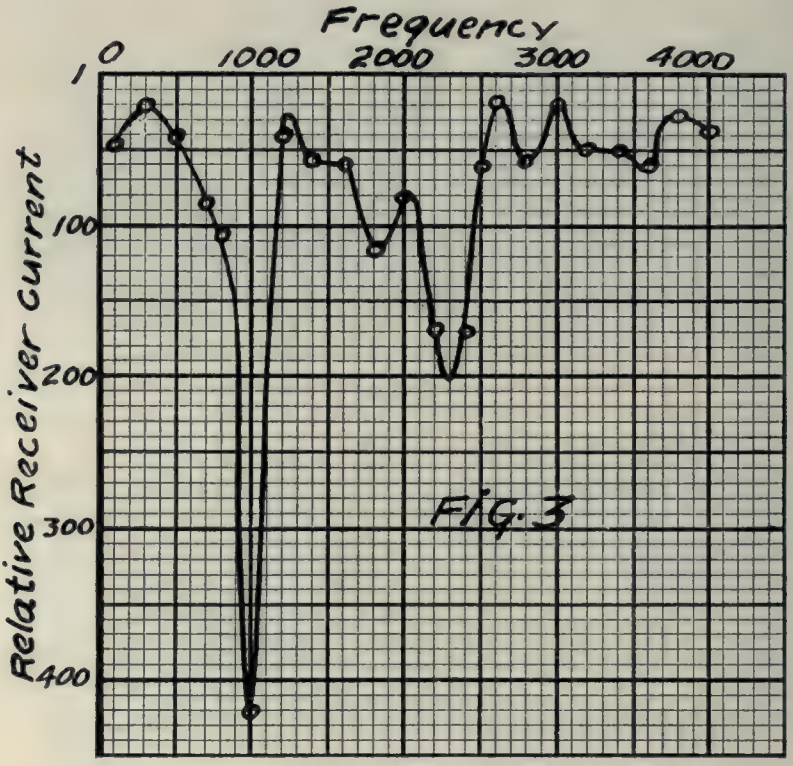

Chart 3.—Curve for left ear of patient, aged 27, with deficiency caused by chronic otitis media since childhood.

receiver currents are squared and then plotted as a function of frequency, the resulting curves will show the relative intensities of the pure tones for minimum audibility of the defective ears compared with the normal. Such curves will give one the correct idea regarding the relative sensitivity that exists among defective and normal ears

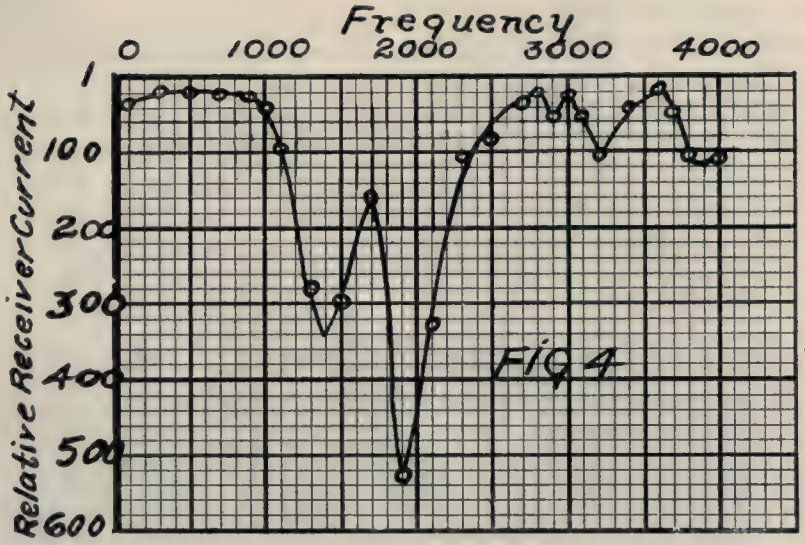

Chart 4.—Curve for right ear of man, aged 42, with bilateral deficiency in hearing.

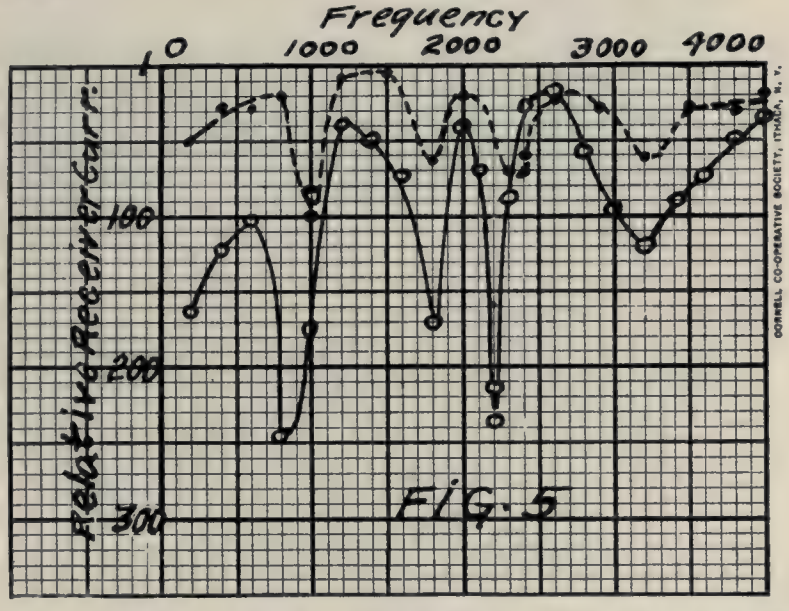

Chart 5.—Curves of hearing of two patients with otosclerosis, upper curve that of girl aged 13, lower curve that of patient aged 34.

at various frequencies. One then begins fully to realize that the normal ear is an extremely sensitive apparatus, possessing a sensitivity of the same order of magnitude as is possessed by the eye.

The curve shown in Figure 3 is that of the left ear of a patient (aged 27) who has had deficient hearing in that ear dating from chronic otitis media in childhood. Tests showed middle ear deafness. The drum was little thickened, but the malleus was attached to the inner wall of the middle ear. Tinnitus was present only occasionally. The whispered voice was heard at 6 inches.

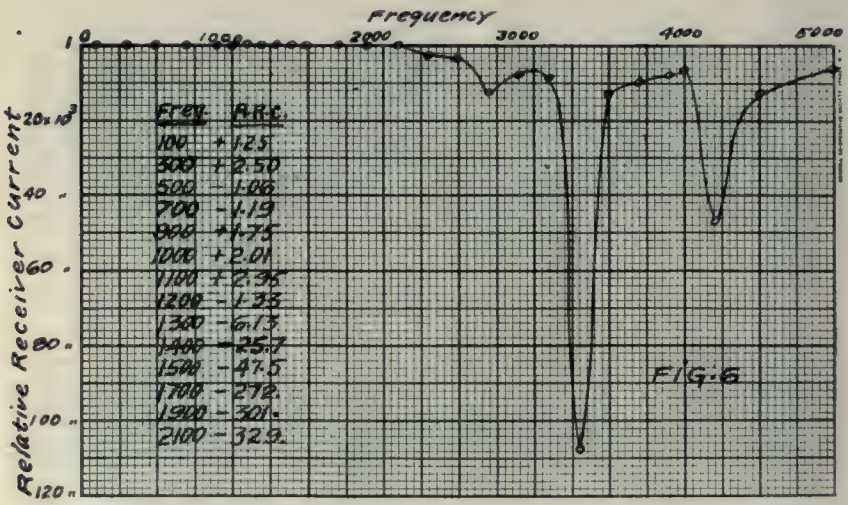

Chart 6.—Curve of hearing of patient 54 years old with nerve deafness.

As shown by the curve, the displacement of the drum membrane and the chain of ossicle bones so far from their natural positions had caused a large depression in hearing, between 800 and 1,200 d.v. which is the most important region for speech sounds. The result was that the hearing of this patient was defective for speech sounds, but for other frequencies the deficiency was not so great. There was considerable depression in sensitivity extending from 1,500 to 2,500 d.v. This curve clearly shows that the pathologic changes in the ear had not caused the same depression at all frequencies. If the curve were plotted to show the sensitivity at various frequencies, as in Figures 1 and 2, one would not find the large increase in sensitivity in the region of 2,000 d.v. that exists in normal ears. This statement also applies to the region of 1,000 d.v.

The curve shown in Figure 4 is for the right ear of a man of 42 years of age whose deficiency in hearing (bilateral) was first noticed 5 years ago. The right ear showed a marked relaxation of the drum membrane in the posterior half. Whispering was heard at 10 inches. The tests showed middle ear deafness, with deficiency in perception of the upper tones. These was no paracusis.

The type of curve for this case is quite different from that shown in Figure 3. There is no depression at 1,000 d.v. (that is, relative to the rest of the curve), but there is a region of a large decrease in the degree of hearing extending from 1,000 to 2,500 d.v. This is the region in which the normal ear has a pronounced maximum; hence, relative to the normal ear there is a marked decrease in this region. It suggests, that the absence of tension throughout the center region of the drum membrane to which the malleus is attached prevents the sound waves from transmitting their energy to the internal ear by means of sympathetic vibrations of the drum membrane and the attached ossicle bones. This indicates that the large increase in sensitivity of normal ears in the region of 2,000 d.v. is due to the resonant characteristics of normal ears.

In Figure 5 are shown two curves of patients suffering from otosclerosis. The upper is that of a girl of 13, with a normal drum membrane, open tubes, bone conduction increased and negative Rinne, with a deficiency in hearing of lower notes and some loss of perception for upper notes. A whisper can be heard 1½ yards; the acumeter at 6 yards. The lower curve is that of a patient, 34 years of age, with deafness of at least 17 years' duration. A whisper could be heard at 8 inches; the acumeter at 2 yards.

The two curves are exactly alike except for magnitude. The upper curve, for the 13-year-old girl, shows that the method of testing gives reliable results for young people. Several curves have been taken for this type of deafness, and the general characteristics are the same for all of them, so long as the disease has been confined to the middle ear. In general, the depression is much larger at the lower frequencies than at the higher ones. There are also the regions of large depressions confined to certain frequency ranges.

In Figure 6 is given the curve of hearing of a patient with nerve deafness. The patient was 54 years old and had noticed bilateral deafness for at least 5 years. Both drums were thickened. The eustachian tubes were open. A whisper was heard at 20 inches and

the acumeter at 8 inches. The Rinne test was positive and bone conduction was diminished. Low notes were heard well but upper notes were not perceived. Slight tinnitus was present but was not troublesome. There was no paracusis.

This curve for so-called nerve deafness shows the surprisingly large variations that exist at the various frequencies. Reference to the data given in the table shows that the relative receiver current up to 1,200 d.v. is on the average about 1, that is, the ear is about normal up to this frequency. Above this frequency the decrease in sensitivity is rapid, especially between 3,100 and 3,500 d.v. This large decrease is of such a nature as to allow the conclusion to be drawn that the disease is not one that has affected a system vibrating as a whole, but one that has affected parts of the ear which are of fundamental importance in audition, and which are loosely coupled to each other and to the rest of the ear. Thus at 3,300 d.v. it requires a vibrational energy which is about 12 billion times greater for the patient to hear than it does for a normal ear to hear, without affecting the region below 1,200 d.v.

A number of curves for nerve deafness have been taken and these data enable us to draw conclusions of importance. It does not seem advisable to attempt at the present time, however, to go into a theoretical discussion of these and other data obtained.

In conclusion, we indicate briefly the theoretical bearing of these data.

1. The existence of the maxima in sensitivity for normal ears shows that they function at the threshold of audition, like an ordinary mechanical system, possessing the same kind of characteristic factors that control such systems. 2. The internal ear functions as though it were laid out in a linear fashion as regards its frequency range, and the data confirm the physiologic teaching that the region of highest frequencies is nearest the stapes and progresses to lower and lower frequencies toward the apex of the cochlea. 3. The internal ear functions not as a single vibrating system, such as a membrane, but as a complex system each member of which is loosely coupled or connected to the rest of the system. 4. There are considerable data at hand to indicate not only that the power of pitch perception lies in the nerve ending, but also that a small group of nerves responds to a small range in frequency. That is, each nerve, including its ending, responds to only one narrow range in frequency and to no other frequencies.

There are other conclusions that we might indicate, but it seems best, as already pointed out, that we should first secure much additional data. However, the statements made seem to show that the present research, of a cooperative nature, when carried further promises to yield results which will throw additional light on many problems connected with hearing both in normal and defective ears.

PHYSICAL FACTORS UNDERLYING THE USE OF RADIUM AND RADIUM EMANATION

GERALD L. WENDT

January 28, 1921

THE RADIATIONS FROM RADIUM SALTS

The complexity of the radiations from an ordinary tube of radium can hardly be overemphasized. The mere division into three classes—alpha, beta, and gamma—is only a preliminary step, for there are present in every such tube at least seven, and usually more, distinct elements, each of which has its own characteristic rays, of one, two, or even all three of these classes, and each of these is incomprehensibly complex. In the clinical use of radium this complexity is often lost sight of, a fact which has hampered the development of radium therapy.

It is well known that these rays arise from the explosions of the radioactive atoms themselves, and that we are here dealing with a source of energy quite different from the usual types. Realization of the amount of this energy is not so common. Radium keeps itself constantly 2 or 3 degrees above the temperature of its environment, due to the absorption of its own rays. The heat thus evolved amounts to about 134 gm. calories per hour from a gram of radium in equilibrium with its decomposition products. Of this, 25 calories come from the radium itself, and 109 from the gaseous emanation and its products. A brief calculation shows that 1 c c of the emanation under these conditions gives no less than 24,300,000 calories before it ceases radiating energy. That this is a stupendous quantity of energy can be shown by comparison with the heat liberated from an ordinary chemical reaction. One c c of mixed hydrogen and oxygen gives, in one of the most energetic of all known chemical reactions, 2 calories. The same quantity of radium emanation gives more than 10,000,000 times this quantity. Obviously the two are not comparable. In the one case we are merely scratching the surface of the atoms. In the other, deep-seated changes take place, and a large fraction of the total energy contained within the atom is made available. Radioactive change of one element into another is a wholly different thing from a chemical reaction. Even the analogy of comparing the chemical heat with the water evaporated from the surface of a watermelon and the radioactive energy to the entire water content of its interior falls far short of the truth.

The Structure of the Atom.—The anatomy of the radium atom needs to be understood before the distinction becomes clear. This was first deduced by Sir Ernest Rutherford, who concluded that almost the entire mass of an atom is concentrated in a dense nucleus at its center. This nucleus theory of the atom has been elaborated mathematically, and has furnished the explanation of so many otherwise unintelligible phenomena that it is now almost universally accepted. According to this theory, the diameter of the nucleus is about 10^{-13} cm. This is only one-hundred-thousandth of the diameter of the hydrogen atom, 10^{-8}, yet practically all the mass of the atom is condensed into this nucleus. The outer part of the atom is composed of rings of electrons in rapid motion, like planets about the sun. To these electrons the chemical properties of the various elements are due, and it is with this exterior that we usually deal. In radioactivity, however, we are only incidentally concerned with the electrons: the rays come from the nucleus. It is only by means of the rays that we obtain any information as to the nature, or even the existence, of the nucleus.

The Alpha Ray Disintegrations.—While the planetary electrons are easily knocked out of the atom, the nucleus is very stable in all atoms except those which for some reason are "radioactive." In these the nucleus explodes. Of course, each radium atom can explode only once, for what remains cannot be radium; it is, in fact, quite a different substance. Whether any individual radium atom "lives" for a second or for millions of years is a matter of chance. But with the enormous number of atoms in a gram this chance becomes a certainty, and the number of radium atoms which explode per second is strictly proportional to the number present. Of every million radium atoms present at any time, 346 will explode per year, or about 0.00001 per second. With 100 billion radium atoms, one explodes per second. Since there are 10^{21} atoms in a grain of radium, however, such a gram gives 10,000,000,000 such explosions per second. This means that in about 1800 years any quantity of radium will have been reduced to one-half its original amount.

As stated in the foregoing, the energy liberated in these explosions is tremendous. What happens is the ejection from the nucleus of a smaller nucleus, 4 units in atomic weight, at a velocity of 1.6×10^9 cm. or about 10,000 miles per second. All radium explosions emit these particles, the "alpha rays," which are really nuclei of helium atoms, at this same velocity. On encountering material obstacles they give up

their energy in collisions and are reduced to a velocity such that we can no longer detect them when they have gone through 3.3 cm. of air. Since they all have the same velocity they all go the same distance before they are lost, so that this distance is characteristic and is known as the "range."

What remains of the original radium atom is of course projected in the opposite direction, according to the laws of momentum, at a velocity which is relatively smaller because of the greater weight of the particle, namely, 222 units of atomic weight, radium itself having an atomic weight of 226. These are the "recoil atoms." They are no longer radium. Not only has the nucleus lost 4 units of weight in the explosion, but also, since it is composed of positive electricity and 2 units of positive electricity go off with the helium nucleus, what remains is negatively charged due to the excess of electrons on the outside of the atom. This cannot last, however, and 2 electrons at once drop off. But these are valence electrons, and hence the new atom has a valence 2 less than the radium. Now radium is in the group of the periodic system with barium and has a valence of 2. The new atom therefore has a valence of zero, and is, in fact, a member of the group of noble gases in the periodic system, along with neon, argon, etc. It is called niton, or more usually radium emanation. Why it is a gas rather than a solid is not clear, but it is in every respect a chemically inert gas just like the other gases of that group.

These atoms of the emanation are much less stable than those of radium. One out of every 500,000 explodes per second, and any quantity is thus reduced to half value in a little less than 4 days. Starting with pure radium, there will of course be no alpha rays from the emanation, and during the first minutes after purification the emanation will be so small in quantity that the rays from it will be only a small fraction of those from the radium. As time goes on, however, more and more rays come from the emanation. Take 100 billion radium atoms to start with. One explodes per second. When 500 have thus been converted into emanation the latter will be exploding at the rate of one every thousand seconds. By the time 500,000 atoms of emanation have formed, they will be exploding at the rate of one every second. Hence they are exploding as fast as they are formed. No quantity in excess of these 500,000 can thus be accumulated at any one time from this amount of radium. The two are said to be "in equilibrium." This will occur within a month after all the emanation has been separated from the original radium.

The emanation has a shorter life than the radium. This is accompanied by a greater energy of explosion. Its alpha rays are projected with a velocity of 1.7×10^9 cm. per second and have a range of 4.2 cm. in air. They all have the same velocity and range, but this is different from the range of radium itself. The range of the alpha rays can thus be used as a test to distinguish the two substances. Indeed every radioactive substance that emits alpha rays has its own characteristic range, dependent only on the energy with which it explodes.

The product of the explosion of the emanation atom, called radium A, has an atomic weight of 218 and is again two places to the left in the periodic system. It is thus in the sixth group, since the zero group and the eighth group are chemically the same in this regard. It thus resembles tellurium and has a valence of 6. It also is unstable, even more so than the emanation. One out of every 250 atoms explodes per second, so that it is reduced to half value in 3 minutes. Thus for every 500,000 emanation atoms, and for 100 billion radium atoms only 250 atoms of this radium A can be formed before it decomposes as fast as it is formed. It rapidly reaches equilibrium, and emanation is thus never handled free from it. It can, however, be distinguished by its longer range, which is 4.75 cm.

In a similar way the life periods and ranges of the one further product that gives alpha rays, radium C′, can be distinguished. Radium B is an intermediate product which does not give alpha rays on exploding, and will be discussed later. After radium C′ comes radium D, whose period is so long and whose activity is therefore so small that it need not be considered.

Thus, every sample of radium in a sealed tube gives out 4 different kinds of alpha rays, corresponding to the 4 different successive products which break up with the emission of the helium nucleus. If the products have reached equilibrium with the radium, as occurs within a month, there will be 4 alpha rays emitted for every radium atom that explodes. Similarly, the emanation separated from radium will reach equilibrium with its products within 3 hours, and will then give 3 alpha rays for each atom of emanation which explodes.

Use of Alpha Rays.—While these explosions in which alpha rays are emitted are the most violent of the radioactive transformations and give about 93% of all the energy that is lost by radiation, this energy can only rarely be used. These rays are effective in producing many chemical reactions, such as the formation of ozone from oxygen, of

hydrochloric acid from hydrogen and chlorine, etc. But for this purpose the radiating substance must be exposed directly to the reacting substances. The walls of an ordinary container would absorb the alpha rays completely. It is possible to use the gaseous emanation in glass tubes so thin that the rays pass through, but the glass may be no thicker than a sheet of tissue paper. If the alpha rays from radium are to be used, the radium must be applied directly or through a very thin coat of varnish. Since the alpha ray of maximum range in air penetrates only 7 cm. of air, and the stopping power of a substance is roughly proportional to its density, and finally, since the density of ordinary materials is about 1,000 times the density of air, it follows that the rays cannot penetrate more than 0.007 cm., or less than 0.1 mm. of any solid or liquid. The penetration is, in fact, only a few hundredths of a millimeter. Only carefully designed "direct applicators" therefore allow the use of these rays.

Furthermore, the rays are of no value except in the treatment of superficial growths, since they cannot penetrate into the tissues. Obviously, as in all chemical reactions, the application of energy to a system has no effect unless that energy is absorbed by the system. A perfectly transparent substance can never be changed by light. So also if the deeper layers have no opportunity to absorb the alpha rays, they can have no effect.

For these reasons we are not concerned as to the possibility of separating the three or four different species of alpha rays from each other. This can be done by interposing very fine screens which absorb the weaker rays and allow the faster ones to pass, but this has no practical purpose.

It is important, however, that the alpha rays can be thus easily absorbed and removed from the more useful beta and gamma rays. Indeed, care should be taken when the latter rays are used that all the alpha rays are absorbed, since they otherwise cause severe surface burns, being about ten times as effective where they do go than are all the other rays together.

The Beta Ray Disintegration.—It has been stated in the foregoing that radium A, which gives alpha rays and is reduced to half value in only 3 minutes, produces radium B. Since the former is in the sixth group of the periodic system, the latter is in the fourth group, being analogous to lead, though it has an atomic weight of 214. This substance is also unstable. Its explosions, however, are of quite a different

nature from those of the elements we have heretofore considered. It explodes rapidly, so that it is reduced to half value in slightly less than half an hour. It does not emit alpha rays, however. All the characteristics of the previous elements are missing. In their stead we observe the emission of rays that are much more penetrating, but which have individually much less energy than have the alpha rays. It has been shown that instead of being positively charged, they are negative, and instead of being of atomic size they are several thousand times smaller. They are, in fact, electrons, and are identical with the atoms of electricity which constitute an electric current when they flow through a wire or through an air gap.

These electrons differ from all other known electrons in their tremendous velocity. Some of them are ejected from the atoms of radium B at a velocity which is 99.8% of the velocity of light; that is, more than 180,000 miles per second. To give an electron such a velocity in air requires a potential of several hundred thousand or even million volts. This fact alone indicates that these electrons, or beta rays, do not come from the surface of the atom, but from its nucleus, where the forces are condensed and sufficiently intense to account for these high velocities.

While the amount of energy carried by each one of these beta rays is less than 1% of the energy of the much larger alpha particle, its velocity is so high that it penetrates considerable thicknesses of matter. They can be detected after passage through as much as a meter of air. They pass through as much as 3 cm. of aluminum. This is due to their velocity and their small size, which allows them to pass through the majority of atoms without encountering material resistance. As stated, the aggregate space occupied by an atom is probably less filled with matter than is the space occupied by the solar system. Like meteors in the astronomical analogy, they can therefore pass through what we consider solid matter with relatively few collisions.

The Gamma Rays.—The emission of beta rays is invariably accompanied by the emission of gamma rays. These latter are radiations in the true sense, i. e., they are not material particles, as are the first two classes mentioned, but are ether waves, similar to light and roentgen-rays. They are distinguished from roentgen rays only by being much shorter in wave-length. Visible light waves are between 0.0007 and 0.0004 cm. in length, or in the more usual units, between 7,000 and 4,000 Angström units. As the wave-length of light decreases all matter

becomes more opaque to it until at about 1,300 A. U. all solids are entirely opaque. Much shorter wave-lengths, however, again penetrate, and when we reach a length of only 1 A. U. we have roentgen rays with their extremely great penetration. The shorter the wave-length the more penetrating a roentgen ray is. Hence the gamma rays, which are in fact roentgen rays with a wave-length of about 0.1 A. U., are the most penetrating of all known rays.

They are generated in the radium just as roentgen rays are generated in a tube. In the latter case a stream of electrons is projected through an evacuated space under a high potential, and thus strikes the material of the anticathode or target at a high velocity. The energy of the collision is radiated largely in the form of short-wave radiation or roentgen rays. The intensity of the roentgen-ray emission depends only on the number of electrons passing, i. e., on the milliamperage. The wave-length of the roentgen rays, however, depends on the velocity of the electrons, i. e., on the potential or the spark-gap. The higher the potential the greater the frequency and the less the wave-length of the roentgen rays. It is, of course, well known that increase of potential gives "harder," i. e., more penetrating and thus shorter wave-length roentgen rays. The conditions within the radium tube are the same. Atoms of radium B and of radium C are constantly exploding and sending out the electrons in the form of beta rays. These collide with the atoms of the various types of radioactive elements present in the tube, and the energy of the collision is similarly radiated in very short waves. But since the energy with which the electron is sent out is much higher than from any potential obtainable in a roentgen-ray tube, the rays thus generated have a correspondingly shorter wave-length. The extremely penetrating gamma rays from radium B correspond to a potential of 200,000 volts, and presumably it is an intra-atomic field of about this strength that projects the beta ray electron.

The beta rays from radium B fall into about 30 different groups of velocities, and thus there are also many groups of wave-lengths in the gamma ray spectrum of this substance. In addition, radium C is present in every radium tube and contributes its own types of gamma rays. Finally, since the velocities of the beta rays are continuously reduced before they finally emerge from the tube, there is also a general distribution of gamma ray wave-lengths, a continuous spectrum.

While the potentials within the radioactive atoms are higher than those conveniently attainable in roentgen-ray work and the gamma

rays are thus more penetrating than roentgen-rays, the intensities of the latter can be made much greater than those of gamma rays. The intensity of such radiation is proportional to the number of electron collisions, and thus can be increased at will to very high values in roentgen-ray tubes, while any one radium tube gives a constant intensity dependent only on the amount of radium B and C it contains.

The Use of Beta and Gamma Rays.—Both these rays may be used in therapy, but the beta rays can never be used without the gamma. Since the latter are so much more penetrating, they cannot be separated from the beta rays by fractional absorption, and since they are light waves they cannot be deflected or removed by other means. Beta ray treatments must therefore count on the presence of the more penetrating though less powerful gamma rays. The energy of the gamma rays is only about 1% of that of the beta rays. For beta ray treatment the radium tube must be used almost bare, i. e., it must not be inclosed in lead. Three to four millimeters of lead will completely absorb the beta rays. A bare tube will give a beta ray penetration of about 2 to 3 cm. in tissue.

This penetration is so low that the gamma rays are much more useful. For effective use without danger of surface burns the tube is covered with a layer of lead to absorb the beta rays. Since gamma rays are more penetrating than roentgen rays, the question of their effective range is only one of intensity. Their energy per square centimeter of course decreases with the square of the distance from the tube, as with all other radiations, and hence to reach deep regions it is often necessary to use "cross fire" methods such that the spot aimed at received repeated doses from various angles, while surrounding tissues are radiated only once from some one of the points of application. When a tube is inserted in a body cavity and the rays are to be used in one direction only, the back of the tube must be covered with heavier lead to prevent the escape of intense radiation. While even a centimeter of lead does not absorb the gamma rays completely, their intensity may thus be cut down to a point below that of effective dosage.

The ability to apply the tube directly to the surface of the lesion in this manner is of course one of the advantages of radium therapy. Because of the inverse square of the distance law, however, in such usage the intensity and therefore the effectiveness of the rays dies off rapidly. When the tube is at some distance from the lesion this is not

true, and a uniform dose may be given to a large area. It should be noted that this law of decrease holds only for light radiations and is not exactly applicable to the material rays like the beta.

One more point should be mentioned. There is a close relation between the electrons which cause roentgen and gamma rays and beta rays. The reverse process is equally common. Thus the passage of either roentgen or gamma rays through matter liberates large numbers of electrons. In the case of the very high frequency gamma rays these liberated electrons themselves attain high velocities, and are, in fact, powerful beta rays. This is also true of the roentgen rays, although the frequency of the ray is less and the velocity of the liberated electron is also less. Furthermore, the roentgen-ray tube is commonly at some distance from the point under treatment, so that these secondary electrons are dissipated. With a radium tube, however, they may be liberated at the very surface of the lead covering which excludes the primary beta rays, and may thus cause a surface burn in spite of heavy lead protection. For this reason the lead tube should be placed within a thin rubber tube. This will absorb the secondary beta rays from the lead, and will itself emit very few electrons under the action of the gamma rays.

The chemical and therefore the therapeutic action of the beta and gamma rays is much the same, and they may be used interchangeably when their penetration and energy are borne in mind. It will be noted that the beta and gamma rays are evolved exclusively by radium B and radium C and not by the radium itself. These beta radiators are themselves products of the radium emanation, a fact which has lead to the wide use of the emanation itself in place of radium tubes.

THE USE OF RADIUM EMANATION

It has been pointed out that the alpha rays, while they are the most powerful, are practically useless because of their extremely low penetration, and that for therapeutic purposes only the gamma rays are useful. Hence it is obvious that the radium itself is of no therapeutic use, except as it furnishes radium B and C, for the gamma rays come only from these two elements. Since the only function of the radium is to produce radium B and radium C, it would be advantageous to keep the radium in a secure place and to extract from it these active elements.

This can readily be done by employing the physical properties of the radium emanation. As has been stated, this is a gas analogous in

every way to the gases of the zero group of the periodic system, such as neon and argon. Because of this fact it can easily be separated from radium. Solid radium salts lose their emanation constantly and slowly, but not completely. In order to drive the emanation entirely from a radium salt, the latter must be heated to a high temperature. When, however, a radium salt is dissolved in water, the emanation collects in the water and above it, and it may readily be pumped out and sealed into containers for use.

During the conversion of radium into the emanation only alpha rays are emitted. The gamma rays are thus still to come in subsequent changes, and if the emanation is sealed into small tubes it will there disintegrate to give radium A, B and C, and the tube will thus rapidly become a source of gamma rays.

The Quantity of Emanation Produced.—It has been stated that of every 100 billion radium atoms one explodes per second, and that of every 500,000 emanation atoms one explodes per second. Hence when the original 100 billion radium atoms have produced 500,000 emanation atoms, the latter are exploding as fast as they are formed—one per second—and this quantity of radium can never accumulate a greater quantity of emanation. These 500,000 will of course not be the first 500,000, since these will constantly have been disintegrating. At first the accumulation of emanation will be relatively rapid, since the few then present will be slow in disintegrating. But as the figure of 500,000 is approached, the speeds of formation and of disintegration become more and more equal, so that near the end of the period the effective accumulation of the emanation is very slow. About one-sixth of the final "equilibrium" quantity is accumulated in the first day, and about one-half by the fourth day. At the end of a month the equilibrium is complete.

The quantity of emanation thus accumulated by one gram of radium at equilibrium is known as one curie, and occupies a volume of 0.0006 c.cm. Similarly, a milligram accumulates during a month one millicurie. Thus also each milligram produces 0.16 millicurie during the first day and 0.5 millicurie during the first 4 days after the emanation has been removed. A quantity of 100 mg. therefore produces 16 millicuries in one day, about 50 in 4 days, and 100 in 30 days.

According to this law of accumulation, it is advantageous to pump off the emanation as often as once a day. For example, if 100 mg. of radium are at hand, 16 millicuries may be removed after one days'

accumulation. After another day 16 more will be available, but the first will have decayed to a value of about 13; thus the two together have a value of 29. This total value must be the same as the quantity which would have been obtained from the solution at the end of the second day with no extraction of the first day. The advantage of daily pumping, however, is that, while the total quantity is the same, one whole day's use was obtained from the 16 millicuries pumped the first day.

Tabulating thus the quantities furnished by 100 mg. in solution throughout a week, the advantage of this method is obvious.

TABLE 1

VALUE EACH DAY

Sun.	Mon.	Tues.	Wed.	Thurs.	Fri.	Sat.	Sun.	Mon.
16	13	11	9	8	6.5	5.5	4.5	4
	16	13	11	9	8	6.5	5.5	4.5
		16	13	11	9	8	6.5	5.5
			16	13	11	9	8	6.5
				16	13	11	9	8
					16	13	11	9
						16	13	11
							16	13
								16
16	29	40	49	57	63.5	69	73.5	77.5

The total quantities represented by the combined activities of all tubes on hand on any day represent the amount of emanation which could have been extracted on that day if none had been taken from the radium in the interval. Thus, after a day about one-sixth is available; after 4 days, one-half; after a week about three-fourths; after 2 weeks, about 90%, and after a month practically the entire equilibrium quantity of 100 millicuries. The figures are only approximate, and do not allow for the inevitable loss of about 5% in the process of extraction.

After a week each tube has decreased to about one-fourth of its original activity, and in the cases cited is too weak to be of much therapeutic value. Several such tubes are then conveniently mounted together in a frame or on a strip of tape to give an applicator of their combined value but distributed over a greater area. Or they can, with proper apparatus, be opened and their combined contents can be introduced again into a single tube with practically no loss. In the continuous use of the emanation extraction apparatus with daily removal of the gas, 92 to 96 millicuries would at all times be available, distributed in tubes of various strengths as indicated. In the case of larger quanti-

ties of radium the quantities of emanation would of course be proportionately increased.

In order to follow the extraction work accurately and to insure proper dosage in treatments, it is extremely desirable to have at hand one of the various types of measuring instruments. Instruments have been devised which will show on a scale reading directly in millicuries the value of each tube by simply placing it in a receiver at the proper position of the instrument. Such instruments can be conveniently used by nurses and others not skilled in radioactive measurements.

Convenience and Applications of the Emanation Tubes.—The chief argument for the use of the emanation rather than the radium itself is the insurance against loss of the radium. The latter is kept securely locked in a safe, and is at no time in serious danger of loss. In practice radium tubes are frequently removed with bandages, or work their way loose, or are misplaced. If this happens in the case of an emanation tube, there is no real loss, since the tubes have no intrinsic value and would decay to worthlessness in a few days in any case. Thus the entire gamma ray activity of the radium is at all times available, with no risk whatever.

There are, however, other arguments in favor of the use of the emanation. It can be concentrated into extremely small volume. Sixteen millicuries of emanation can be put into a tube with a total diameter of 0.5 mm. and a length of 5 mm., which is far less than the size of a capsule containing 16 mg., the corresponding quantity, of radium salt. This is often a critical factor in their application. An emanation tube can, for instance, easily be introduced into a trochar and inserted into body cavities by puncturing or otherwise when a similar procedure in case of the large radium tube would be out of the question. Greater flexibility is also possible, since the tubes can be made of any size or shape and, furthermore, can be arranged in applicators of any desired strength by combining tubes of various strengths either in one tube or by distributing them over any desired area.

There are several precautions which have not yet been mentioned. One is that the gamma rays do not come from the emanation itself, but from the products of its disintegration; i. e., from radium B and C. Hence when the emanation is first introduced into the glass tubes it is free from these products and gives no beta or gamma rays. These rapidly develop, however, and in the course of 3 hours radium A and B have reached their equilibrium quantity so that the tube is at its full

gamma ray strength. Another necessary precaution is the enclosure of the extremely fragile tiny glass tubes within steel needles or other protective covering when in use. Such a needle need not exceed a millimeter in diameter, even for 50 millicuries of emanation.

Other Applications.—The emanation extraction apparatus allows still further variations. In case of surface treatments it may become desirable to make a direct application of a strongly radioactive preparation which makes use of the alpha and beta rays. For this purpose sheets of silver or of copper may be inclosed in a glass vessel and allowed to stand in contact with the emanation for several hours. They will thus take up a deposit of radium A, B, and C, which serves as an extremely active source of radiation while these elements last, which is about three hours. Very fine needles may thus be activated for work in confined areas.

Furthermore, radioactive preparations for intravenous or other injections may be prepared by similarly exposing sodium chloride to the emanation and allowing it to take up these active elements. The solution of the salt for injection is then temporarily strongly radioactive. Such solutions are not subject to the objections that apply to the injection of radium itself, for the question of their elimination by the system is not involved. In the course of three hours their activity dies out almost completely, and if longer treatments are desired the injections must be repeated.

Finally, in the case of massive tumors it is occasionally desirable to give a prolonged treatment. This can be done by inserting or burying the emanation tube within the mass of the tumor and allowing it to remain until its activity is lost or until the tumor is removed.

HISTOCHEMICAL STUDIES ON THE MECHANISM OF RENAL SECRETION

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The multitude of views concerning the true mechanism of renal function falls into two categories of general, conflicting opinions or schools. The one, first suggested by Ludwig, assumed the glomerulus to be the seat of chief activity, and the urine to be a filtrate from that organ. To this Cushny has added the idea of reabsorptive activity by the convoluted tubules, thereby explaining the concentration of the urine and the retention of threshold bodies, such as sodium chloride. The other view, bearing the joint names of Bowman and Heidenhain, lays stress on the process of secretion of solutes by the convoluted tubules, these structures thus raising the concentration of the urine.

The problem which presents itself, therefore, in its simplest form is the determination of the direction of progress of the electrolytic urinary components as they pass through the cells of the convoluted tubules. To study this progress with electrolytic salts rather than with colloidal dyes, as has been done heretofore, is desirable because salts are substance normally secreted into the urine, while the dyes are obviously foreign. In our experiments iron was chosen for the work because: 1. It is normally secreted. 2. It is very readily detected in minute quantities by the Prussian blue reaction. 3. There is no free (detectable) iron normally in renal tissue. 4. It forms nontoxic salts. The green ferric ammonium citrate was found most satisfactory, the more commonly known red salt being much more toxic because of an unsaturated carboxyl group.

In studying the mechanism of iron elimination by the kidney, two questions are to be considered: 1. What is the route of the iron in its passage? 2. What does the iron do to the kidney? Series of experiments were carried out along the following lines: Large doses of ferric ammonium citrate were injected intravenously into rabbits and the animals killed at various intervals following the injection; the kidneys were at once fixed in 95% alcohol and paraffin sections prepared and

the Prussian blue precipitated by treatment of the sections with sodium ferrocyanide in dilute acid solution. The time ranged from 0.5 minute to several days. A series of such preparations at 0.5, 1, 2, 3, 5, 7, 10, 12, 15, and 20 minutes and more showed the direction of movement of the iron through the convoluted tubules as the multiple exposures of a cinema reveal motion. The fine blue particulate granules of Prussian blue first appeared at the basal pole of the cells at 1 to 3 minutes. After from 3 to 5 minutes it had progressed to the level of the nuclei and after 5 to 7 minutes it reached the free border and entered the lumen. After that time the greatest intracellular concentration of iron was always just under the brush border at the lumen. In the several hundred sections studied iron was never seen in the spaces of the glomerular capsule. This series adds further evidence to the conception of a secretory function of the convoluted tubules.

Not all the iron reaching the kidney is eliminated, however. The urine becomes negative for iron in about 5 hours, but long after that, for several days in fact, there is iron in the convoluted tubule cells. It is practically all just under the brush border, indicating a marked cellular polarity. Furthermore, this retention of iron is accumulative if the animal is given multiple injections over a period of weeks, and this accumulative retention has distinct effects on renal function: 1. There is a constantly increasing period of elimination of the iron with each further administration, the secretion being slowed by the block. 2. There is a decrease in the quantity of iron eliminated with each new injection. 3. There is a marked fall in the ability to secrete phenolsulphonephthalein after several injections of iron.

The effect of the iron on the renal processes was the most interesting phase of the subject. 1. Iron does not appear in the bladder urine before 10 minutes after injection. 2. Its concentration rises quickly and falls slowly until after about 5 hours there is no more iron. 3. There is at first a brief transient diuresis, and then, during the height of iron elimination there is a marked fall in the water excretion, which only rises again as the iron disappears. We found this fall entirely unassociated with blood pressure or temperature changes. Furthermore, during the elimination of iron there always was: (1) a marked fall in the specific gravity of the urine, e. g., from 1.020 to 1.008; (2) a disappearance of carbonates from the urine. (Rabbit urine is normally cloudy with carbonates, but during the time iron was

being passed there were none. The urine remained alkaline, the iron being in the form of dark brown ferric hydroxide.)

The explanation of these effects on renal mechanics is correlated with Martin Fischer's views on the mechanism of edema. Ferric ions and citrate ions are markedly active in causing colloids to give up water and prevent colloids from absorbing water. Therefore a diuresis should theoretically result from the injection of ferric ammonium citrate. That the reverse is true is explained by the fact that the iron salt promptly becomes intracellular in the convoluted tubules and there tends to block the further passage of water because the colloids in the cells are inhibited from absorbing water; if the solvent is thus inhibited from passing, so will also be the solutes, which view accounts for the fall in the excretion of water, carbonates and "phthalein" and the reduced specific gravity.

DISCUSSION

E. R. LE COUNT: I would like to ask Mr. Stieglitz whether there is any evidence of a reabsorption of iron. Some views have been advanced that some substances pass into the renal epithelium and then again back into the blood.

A. J. CARLSON: The Ludwig or mechanical theory of urine formation, in my judgment, has not been even debatable the last 15 or 25 years. At that time the accumulation of evidence for the secretion theory was complete. Here is another bit in the same direction. I should like to ask Mr. Stieglitz, in view of the fact that normally little (an infinitesimal amount) of the iron eliminated goes by way of the kidney (it is eliminated by the alimentary tract), whether he could get similar pictures in the mucosa cells of the small intestine.

A. B. LUCKHARDT: I would like to ask whether Mr. Stieglitz lowered the blood pressure so as to rule out filtration through the glomeruli; if he found the blood pressure was low, he could rule out filtration of the glomeruli and the tubules below. It is well known that if the blood pressure drops below 30 mm. of mercury all filtration of the glomeruli stops. If that has not been shown, it is possible that a good part of the urine has been filtered through the glomeruli.

E. J. STIEGLITZ: In answer to Dr. Le Count, I can say that iron was never seen in the glomerular capsules, that it probably entered the urine by the convoluted tubules. For several days after the injection of iron there was still iron in the convoluted tubules. There was never iron in the urine at that time. I cannot say whether it enters the glomeruli.

In regard to Dr. Carlson's question: Sections of the intestinal mucosa and of the spleen and liver were studied following injections of iron. The distribution of that iron following intravenous injection seems to be to the kidney, to Kupfer's cells of the liver and to the cells of the spleen, particularly in the splenic pulp. There was some iron in the mucosa, but the concentration was by no means that which one sees in the urine. This does not prove that the physiologic route of iron elimination is possibly not through the intestine. We are merely using iron as an example of a salt, not really speaking of the normal physiology of iron.

In answer to Dr. Luckhardt's question: Such an experiment was performed in which the blood pressure was low and the iron did come through into the urine, but there was a diminished quantity of urine eliminated. In the reduction of the blood pressure to such a low level as to interfere with glomerular function, it must greatly interfere with the nutrition of the kidney and thereby interfere with the function. If it interferes with glomerular function, the effects on the tubule secretion would also be marked.

STREPTOCOCCI IN CHRONIC INFECTIONS OF THE PROSTATE AND SEMINAL VESICLES

From the John McCormick Institute for Infectious Diseases, Chicago

RUSSELL D. HERROLD

February 25, 1921

There has been much written during the last fifteen years on the clinical and bacteriologic aspects of prostatic infections, with considerable variance in the bacteriologic reports. There has been no attempt to establish a relation between the type of infecting organism and the clinical course of the infection. This phase of the problem I have been studying in a series of cases.

Young, Geraghty and Stevens found streptococci twice in 19 cases; Squier, once in 8; Culver, 6 times in 34. Friedman and others mention staphylococci, streptococci and colon bacilli as the most common invaders in the order mentioned. Fuchs, Belfield, and more recently Vedier, emphasize the frequent occurrence of B. coli as the causative bacterium. Fuller gives the streptococci a prominent place. Hitchens and Brown, in a series of 45 cases, isolated streptococci in 27 instances. Other bacteria found by them were staphylococci in 25 cases, non-liquifying cocci of the staphylococcus group in 34, diphtheroid bacilli in 31, gonococcus in 5, and B. coli in 2. They used 10% ascites agar. I found as a rule the secondary invaders in postgonorrheal prostatitis to be staphylococci, streptococci and diphtheroids. B. coli was found in few cases and proteus more rarely.

The expressed prostatic fluid cultivated from 109 cases was found to contain streptococci in 34%; in 15 cases streptococci persisted on two or more later examinations, one was negative with the second culture.

The greater incidence of streptococci than generally reported by others may be attributed to the use of ascites blood phosphate agar medium which is a very favorable medium for the growth of streptococcus, discrete colonies often reaching a diameter of 3-4 mm.

The number of bacteria in the anterior third of the urethra and particularly in the fossa navicularis make it necessary that great care be used in the collection of material. A solution of potassium mercuric iodide 1 : 5000, which is known to be highly bactericidal for the common

bacteria of the skin, was used to cleanse the glans, and the anterior inch of the urethra was swabbed with this solution, followed by sterile water or salt solution. A part of the urine was then voided, the prostate massaged, seminal vesicles stripped and the expressed fluid collected in a sterile container and several loopfuls immediately transferred to plates. The efficiency of this technic is indicated by the fact that the cultures from the fossa, as well as from normal prostates, thus obtained are invariably sterile.

TABLE 1

FINDINGS IN STREPTOCOCCUS AND NONSTREPTOCOCCUS CASES

	Streptococcus Group	Nonstreptococcus Group
With definite lesions:		
Prostate and vesicles	19	15
Prostate	7	9
Vesicles	3	3
Without definite lesions	9	11
Percentage of pus cell content:		
Less than 25 per cent.	13	21
More than 25 per cent.	25	19
Pus free:		
Number	6	18
Average in months	7	3⅝
Pus persistent at last examination:		
Number	29	17
Average in months	5	3

TABLE 2

RESULTS OF AGGLUTINATION TESTS

	Number of Strains
Change of blood medium:	
Hemolysis	12
Green	13
Bile, insoluble	25
Bile, soluble	0
Agglutination results with 4 monovalent antistreptococcus serums:	
Serum 1	10
Serum 2	6
Serum 3	2
Serum 4	2
Strains not agglutinated by antistreptococcus serums	5

A comparison was made of an equal number of streptococcus and nonstreptococcus cases taken in the order of their occurrence. As summarized in table 1, a slightly greater number in the streptococcus class gave changes which could be detected by palpation; in 6 cases of this class with involvement of both prostate and vesicles there was extreme tenderness and marked perivesicular infiltration. An equally extensive involvement was noted only twice in nonstreptococcus cases. There seems to be a definitely higher percentage of patients with pus in the streptococcus group, and the nonstreptococcus patients appear to recover in a shorter time.

Bile solubility tests were made on all strains used in the agglutination tests. None were soluble.

There were 12 hemolytic strains and 13 green producing streptococci of the 25 used in serologic classification.

A classification of 25 strains of streptococci is being attempted by serologic methods. Monovalent antistreptococcic serum has been produced with 4 strains. The most satisfactory technic so far used is the following: 16- to 24-hour growth on ordinary phosphate ascites agar slant is suspended in from ¾ to 1 c c of salt solution which gives a sufficiently heavy emulsion for distinct results; 0.25 c c of the dilution of the antistreptococcus serum tested is added to small tubes and an equal amount of suspension added. These are placed in the incubator at 53-56 C. overnight, and the results read the next morning. Several strains which gave a flocculent suspension grown on plain blood agar, after several transfers on ascites phosphate agar, gave homogeneous suspensions which were satisfactory for agglutination. Ten strains were agglutinated by serum 1, 6 by serum 2, and 2 each by serums 3 and 4; five were not agglutinated by any of the 4 serums. This work is still in progress, and further agglutination and absorption tests will be made.

DISCUSSION

ARTHUR H. CURTIS: I wish Dr. Herrold would say a few words concerning the number of colonies which he obtained from most of these cases.

D. J. DAVIS: I think these results are very interesting because infections with the hemolytic streptococcus, particularly in the genito-urinary tract, are of quite rare occurrence. I should like to ask Dr. Herrold about the occurrence of streptococci of both kinds in the normal urethra, whether these organisms occur, and in what percentages in the normal prostate and in the normal bladder.

RUSSELL D. HERROLD (closing): In answer to Dr. Curtis: At least half of the colonies were streptococci with an average perhaps of from 20 to 50 colonies per plate. Many of them had more.

Answering Dr. Davis' question: The streptococcus in the fossa of the anterior urethra, as far as I have observed in normal cases, has been more frequently of the viridans type; In the bladder and in catheterized specimens from the kidneys, streptococci are not generally supposed to be frequently found, and I have not found them in many cases. In a few cases in which I found a streptococcus it was the viridans type.

CHANGES IN THE ALKALI RESERVE, SUGAR CONCENTRATION, AND LEUKOCYTES OF THE BLOOD IN EXPERIMENTAL INFECTIONS

EDWIN F. HIRSCH

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The intravenous injection into rabbits of suspensions of typhoid, paratyphoid A and B, dysentery, colon, Friedlander, or Welch bacilli, and pneumococci, hemolytic or nonhemolytic streptococci is followed within 1 to 2 hours by a leukopenia and a diminution of the alkali reserve of the blood. The rapidity and the degree of lowering seem to depend on the pathogenicity of the bacteria used. Following the depression of the alkali reserve and the leukopenia, there is an 18 to 24 hour interval during which the leukocytes rapidly increase in number, and the alkali reserve returns or slightly exceeds the value originally determined for the blood of the rabbit. When the alkali reserve remains depressed, the leukocytosis persists, but later when it returns to or slightly exceeds the normal, the number of leukocytes also becomes normal. In experiments when the bacterial infection does not subside with such simple and prompt changes, there are irregular depressions of the alkali reserve and coincident periods of leukocytosis until both remain normal, and there is no evidence by these tests of disease in the animal.

The results of many experiments of this kind have been similar. This repetition of similar results suggests that lowering the alkali reserve of the blood sufficiently or perhaps some as yet unknown factors associated with its depression are concerned with the production of generalized leukocytosis.

With the changes in the alkali reserve of the blood mentioned, there are without doubt others as yet unsuspected and of a chemical nature, since alterations in H-ion concentration are known to accompany or bring about disturbances in the composition and properties of such an intricate solution of colloids and crystalloids as blood plasma. One of these changes it is fair to suppose concerns the dextrose of the blood, and some hint of the changes in the amount of glucose of the blood is found in the report of Rhodenberg and Pohlman who consider the hyperglycemia of animals immunized against bacteria an index

of the degree of immunization. Elias in 1913 observed glycosuria and hyperglycemia in rabbits and dogs following feeding of dilute hydrochloric acid, while even earlier writers such as Pavy in 1864, Goetz in 1867, and Naunyn in 1868 observed glycosuria following the feeding or injection of phosphoric, lactic, or hydrochloric acid. Underhill, commenting on the effect of acidosis on carbohydrate metabolism, says the introduction of acid into the organism is associated with a disturbance of blood sugar content and is manifested in one direction: namely, blood sugar content is augmented. Other writers have made similar comments.

With these observations as a basis, an experimental study in rabbits was made to determine the effect on the blood sugar concentration of intravenous injections of the pathogenic bacteria previously mentioned, paralleled by estimations of the alkali reserve of the whole blood according to Van Slyke, and by determinations of the number of leukocytes. The sugar of the blood was determined by the Folin and Wu method on 2 c c samples of blood, the total amount of blood taken from the ear veins for each set of determinations being 3 or 4 c c.

The initial lowering of the alkali reserve is accompanied by a sudden and transient increase in the concentration of the sugar of the blood which in degree seems to be in proportion with the depression of the alkali reserve, and seemingly attains its maximum when the lowest level to which the alkali reserve falls is reached. It returns within 2 to 4 hours to the normal concentration even though the alkali reserve remains depressed. These variations are not observed in the blood of rabbits injected intravenously with sterile normal salt solution, or subjected only to the handling and bleeding necessary for the experiments.

Injections of acid postassium phosphate solutions depress the alkali reserve of the blood and produce a hyperglycemia similar to that caused by bacteria. The leukocyte curves in some of these experiments are similar to those produced by injections of bacteria.

Attempts to prevent by subcutaneous injections of carbonate and bicarbonate solutions the depression of the alkali reserve of the blood following injections of typhoid, colon, or Friedländer bacilli were unsuccessful.

The changes in the number of leukocytes were paralleled by determinations of the relative ratios of the various white blood cells. During the early part of the leukopenia stage the percentage of lymphocytes is

somewhat greater than that of the polymorphonuclear leukocytes. In a short time the polymorphonuclear ratio rises so that as the leukocytes increase the percentage of neutrophil polymorphonuclear leukocytes may rise to 80 or 90. Later the lymphocytes form an increasing proportion of leukocytes until finally the normal ration is again reached. When the number of leukocytes decreases rapidly with the return of the alkali reserve to normal, the polymorphonuclear leukocytes seem to disappear first leaving a high percentage of lymphocytes in the blood.

In a number of experiments with injections of acid phosphate solutions, the changes in the number and ratio of leukocytes are similar.

An increase in the concentration of sugar in the blood with acidosis is well known. The occurrence of hyperglycemia with experimental infections seem, then, to depend on a lowering of the alkalinity of the blood, and the degree of hyperglycemia on the extent to which the alkali reserve is depressed.

DISCUSSION

A. J. CARLSON: I would like to ask Dr. Hirsch what explanation he has for the initial fall of the alkali reserve from the injection of these organisms and whether a similar fall will not follow the injection of proteoses or peptones.

JOSEPH L. MILLER: How long does this increase in the alkali reserve continue? I know it continues long after the leukocytes have apparently reached normal.

J. A. CAPPS: The relationship and apparent parallelism between the leukocytosis and the rise or fall of the alkali reserve is remarkable. They seem to be about synchronous in their reactions, that is, the leukopenia and the drop in the alkali reserve take place about the same time. Was this the usual course?

EUGENE CARY: I would like to ask Dr. Hirsch whether he found that injections of glucose had any effect on the alkali reserve restoration.

EDWIN F. HIRSCH: Diminishing the alkali reserve of the blood by intravenous injections of suspensions of living bacteria is, so far as I know, not recorded in the literature. The mechanism involved is not clear to me. No experiments have been made with injections of proteoses or peptones, so I cannot speak about the reactions following the injection of such substances. When the alkali reserve of the blood reaches a higher than normal value following the injection of the bacterial suspension, its return to normal occurs usually within 4 to 6 hours. This transient increase has been noted particularly in experiments when the depression of the alkali reserve has been marked.

Curves indicating a parallelism between variations in the alkali reserve and the number of leukocytes of the blood may be repeated by plotting the results obtained in experiments with all the bacteria mentioned.

In a limited number of experiments with injections of glucose subcutaneously into rabbits the amount of glucose given did not increase the alkali reserve; in fact, it seems with the amount of sugar injected that certain abnormal changes in the metabolism of the animals took place, and the alkali reserve of the blood was diminished.

THE BACTERIOLOGY OF THE ADENOIDS

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The bacterial flora of the nasopharynx has frequently been investigated with reference to the detection of carriers, particularly of the meningococcus. In such examinations cultures were obtained by the assistance of the West tube or a curved wire swab. The results of the various surveys made would indicate that the nasopharynx harbors many dangerous bacteria. It has been generally assumed that these organisms flourish among the vegetations or adenoid tissue of this region. It is, however, surprising to find that no studies have been made with the aid of improved bacteriologic methods to determine the flora of these lymphoid structures.

Pilot and Davis [1] demonstrated that swab cultures of the oropharynx were inaccurate and not a true index of the actual flora in the faucial tonsils, particularly with reference to the hemolytic streptococcus which occurred in 61% of the swab cultures of the surface of the tonsils as compared with 97% from the crypts of the excised tonsils. In order to establish definitely the incidence and number of the common pathogenic bacteria in the nasopharynx and the nasopharyngeal vegetations, a bacteriologic study of the extirpated adenoids was undertaken.

METHOD

The adenoids studied were those removed at the ear, nose and throat ward of the Cook County Hospital from April to November, 1920. The patients were children from 5 to 16 years of age without fever or acute inflammations of the respiratory passages. The adenoids selected consisted of lymphoid tissue revealing varying degrees of hyperplasia. They measured from 0.5 to 1.5 cm. in all diameters, and usually presented from 3 to 6 or more folds. In many union had taken place between the free margins of the folds, leaving slits in the tissue not unlike the crypts of the tonsils. In a few instances fatty débris and cholesterol crystals were found in such depressions, but in

[1] Jour. Infect. Dis., 1919, 24, p. 386.

none was any purulent exudate grossly visible. Macerated adenoids were discarded. These adenoids approached the normal as closely as can possibly be obtained. Cultures were made from the epithelial surface and from the depths of the vegetations between the folds and from the bottoms of the cryptlike depressions. Blood-agar plates, heated blood agar for the isolation of the influenza bacillus and Loeffler's medium for the diphtheria bacillus were employed. In 25 instances the nasopharynx was swabbed through a West tube and cultivated on fresh and heated blood agar.

RESULTS

The common pathogenic organisms were identified and studied; the results are indicated in table 1.

TABLE 1

THE INCIDENCE OF PATHOGENIC BACTERIA IN THE ADENOIDS, NASOPHARYNGEAL SWABS AND TONSILS

Organism	Number of Patients	Adenoids % Positive	Nasopharyngeal Swab % Positive	Tonsils % Positive
Streptococcus hemolyticus	103	61	..	..
	25	..	40	..
	21	..	..	95
Streptococcus viridans	103	89	..	..
	21	..	90.5	81
Pneumococcus	103	65	..	..
Type 2	...	2	..	..
Type 3	...	10.3	..	..
Type 4	21	52.7	71.4	66.6
Mathers coccus	103	17	..	..
Staphylococcus	103	60	..	..
Gram negative cocci	103	79	..	..
B. influenzae (Pfeiffer)	115	40.9	..	53.9
	25	..	40	..
B. diphtheriae	100	12	..	12
Diphtheroids	100	30	..	17
B. mucosus capsulatus	103	14	..	..
B. fusiformis	10	20	..	..

Streptococcus Hemolyticus.—Hemolytic streptococci occurred in 61% in cultures taken from the depths between the folds and of the crypts. In 18 these organisms were quite numerous and in 3 in pure cultures. In their hemolytic properties, morphology and carbohydrate fermentation they conformed to the beta type mostly of the Streptococcus pyogenes group. They were bile insoluble and pathogenic for rabbits in doses of 2 c.c. and for mice in 0.5 c.c. of broth culture. The alpha type was encountered in 20%.

Streptococcus Viridans.—Streptococcus colonies causing methemoglobin formation on blood agar occurred in 89%. They were bile insoluble and did not ferment inulin. On the basis of carbohydrate

fermentation 30% of the strains were of the Streptococcus mitis group, 64% of the Strep. salivarious and 6% of the Strep. fecalis. Streptococci causing neither hemolysis nor green formation were noted in 12%; streptococcus mucosus in 3%.

Pneumococcus.—Bile soluble, inulin fermenting strains were found in 65%. Of these, on the basis of agglutination with specific serums, 85% were type 4, 13% type 3, and 2% type 2. With the exception of 2 strains, the type 3 were culturally like Pneumococcus mucosus.

Mathers Coccus.—Large, moist, often flat, green producing colonies variable in bile solubility and inulin fermentation conforming to the streptococcus described by Mathers [2] in the past influenza epidemic were found in 17%.

Bacillus Influenzae (Pfeiffer).—On heated blood-agar mediums influenza bacilli were recovered in 40.9%, often in large numbers. They were identified as gram-negative, pleomorphic bacilli failing to grow on infusion agar, and showing the characteristic property of symbiosis.

Bacillus Diphtheriae.—From Loeffler's medium granular types morphologically identical with the Klebs-Loeffler bacillus were isolated in 12%, often predominating on this medium, and in pure culture in 2 instances. Two strains were toxin-producing killing guinea-pigs in doses of 1 c c of broth culture, while the antitoxin controls survived. The remainder were relatively avirulent. In this connection it should be noted that the patients whose adenoids gave positive cultures did not have diphtheria.

Diphtheroids. — Organisms resembling closely in their cultural characteristics the diphtheria bacillus, but morphologically different in that they did not show metachromatic granules, occurred in 30%. They were further differentiated by their inability to ferment the ordinary sugars.

Other Organisms.—Staphylococci were noted in 60%, and most of them were of the albus and only a few the aureus type. Gram-negative diplococci were encountered in 79%, appearing chiefly as Micrococcus catarrhalis, Micrococcus pharyngis siccus and a few resembling the meningococcus. A study is now being made for their further differen-

[2] Tunnicliff, R.: Jour. Infect. Dis., 1920, 26, p. 405.

tiation. The Bacillus mucosus capsulatus, growing as large mucoid colonies, was found in 14%. Anaerobic cultures were made of 10 adenoids and the B. fusiformis occurred in 2 (20%).

CULTURES OF THE NASOPHARYNGEAL SWABS OF THE SAME PERSONS

Nasopharyngeal swab cultures were taken from 25 persons before operation. Few hemolytic streptococci were found in 10 persons (40%) as compared with those found in the depths of the adenoids in 15 persons (60%). Influenza bacilli occurred once in the adenoids of a person in this series (44.4%) when it was not recovered from the swab (40%). Pneumococci and streptococcus viridans appeared in the same percentages. It was notable, however, that all of these organisms were decidedly more numerous in the depths between the folds and in the cryptlike depressions than on the epithelial surface and the nasopharyngeal swab, demonstrating the tendency of these organisms, especially the hemolytic streptococcus, to flourish in the recesses of the nasopharynx.

CULTURES OF THE CRYPTS OF THE TONSILS FROM THE SAME PERSONS

The extirpated tonsils of 21 persons were cultivated and revealed hemolytic streptococci in 20 (95%), frequently in predominating numbers, while the adenoids of 15 (71.4%) of these patients contained these organisms in less numbers. The pneumococci were present in 66.6% and the Streptococcus viridans in 81% as compared with 71.4% and 90.5%, respectively, in the adenoids. In those instances in which the pneumococci and green streptococci were absent in the tonsils and present in the adenoids the tonsillar crypts harbored hemolytic streptococci in pure culture. The tonsils of 115 patients were found to have influenza bacilli in 53.9%, whereas the adenoids of the same persons gave positive results in 40.9%. Diphtheria bacilli occurred in 12% of the tonsils and adenoids of 100 children, appearing more often in predominating numbers in the tonsils.

THE INCIDENCE OF HEMOLYTIC STREPTOCOCCI, PNEUMOCOCCI AND B. INFLUENZAE IN THE NASOPHARYNX OF TONSILLECTOMIZED AND NONTONSILLECTOMIZED CHILDREN

Normal children from 5 to 15 years of age, inmates of an orphan asylum, were swabbed in the nasopharynx. After the bacteriologic

work was completed, they were divided in two groups, those who had had their tonsils and adenoids removed from 2 months to 5 years previously and those who did not have either excised. A few children having remnants of tonsils were classified as nontonsillectomized. In 48 with tonsils hemolytic streptococci were recovered in 27 (56.3%) and in 27 without tonsils in 11 (40.8%); influenza bacilli occurred in 17 (39.3%) of 43 persons with tonsils and in 8 of 29 (26.5%) persons without tonsils. J. Meyer found pneumococci in about the same percentage (32.5%) in both groups. It is noteworthy that all of these organisms when present were decidedly fewer in tonsillectomized than in the nontonsillectomized persons.

While the removal of the tonsils and adenoids reduces the incidence and numbers of bacteria in the throat and nasopharynx it is quite evident that it does not cause their disappearance, and that the other lymphatic structure of the oro- and nasopharynx continue to furnish foci for these organisms.

The Flora of the Nasopharynx of Normal Persons.—Every culture taken from the nasopharynx and adenoids showed various organisms. Regardless of the size of the adenoids, or whether or not the vegetations were to be considered normal or markedly hypertrophied, microorganisms, particularly the streptococci, pneumococci and B. influenzae were present, occasionally one predominating over the other, seldom, however, in pure culture. Usually several different organisms were found in the same person in a considerable percentage. It would therefore seem that for children, at least, the organisms commonly encountered should be regarded as part of the normal flora of the nasopharynx, just as we regard certain bacteria as part of the normal flora of the mouth or intestine.

Significance with Special Reference to the Carrier Problem.—On the basis of these results, it is quite apparent that many healthy persons harbor pathogenic bacteria in the nasopharynx, organisms which do not differ from the strains isolated from various pathologic processes of the human body. Can all such persons be termed carriers in the sense that they are sources from which others may become infected? Under exceptional circumstances transmission of hemolytic streptococci from one person to another directly by droplet infection or indirectly through milk, for example, occurs as illustrated in the epidemic streptococcal complications following measles and the milk epi-

demics of streptococcus sore throat. In such instances an epidemic strain of enhanced virulence exists in the throats of the affected persons and those who come in contact with them. Under ordinary circumstances, however, these organisms apparently lie dormant in the tonsils and nasopharynx without harm to the healthy person or to the healthy contact. The carrier state may possibly be limited to persons harboring epidemic strains and to the convalescents and contacts giving positive cultures of the organisms responsible for cases of diphtheria, meningococcic meningitis, and pneumonias due to type 1 and 2 pneumococci. The adenoids, like the tonsils, should be considered as foci where such dangerous organisms may persist.

SIGNIFICANCE OF THE BACTERIA OF THE ADENOIDS AS SECONDARY INVADERS

In the healthy person the micro-organisms apparently exist without doing harm. When, however, the resistance is lowered, either locally by acute inflammations of the respiratory tract as in the exanthemata, pneumonia and influenza or generally by an acute or chronic toxemia or a chronic debilitating disease, these organisms may become a great source of danger. Hemolytic streptococci are commonly secondary invaders in measles, scarlet fever, pneumonia and other primary infections. The pneumococcus, particularly types 3 and 4 and the influenza bacillus are the predominating secondary invaders in influenza. In chronic conditions, such as tuberculosis, nephritis, malignancy, leukemia and other diseases, the streptococcus and pneumococcus are the chief causes of the terminal infection. It seems unlikely that the organisms causing secondary infection in such a variety of conditions are all introduced from without. They may sometimes be acquired from other persons, but it is more logical to assume that many patients succumb to the secondary invasion of the organisms of their own oro- and nasopharynx. It should also be pointed out that from the same sources the complications of otitis media and inflammations of the accessory sinuses of the respiratory tract undoubtedly originate.

SUMMARY

Cultures were taken from the excised adenoids to determine more definitely the flora of the nasopharynx. Pathogenic bacteria were found in every specimen. Of the more important organisms, hemolytic strep-

tococci occurred in 61%, pneumococci in 65%, B. influenzae in 40.9%, B. diphtheriae in 12%. Other streptococci, diphtheroids, staphylococci, gram-negative cocci, B. mucosus capsulatus and B. fusiformis were encountered.

The depths between the folds and bottoms of the crypt-like structures of the adenoids harbored hemolytic streptococci, pneumococci and B. influenzae in larger numbers than the epithelial surface or the nasopharyngeal swabs.

A series of nasopharyngeal swabs of normal children revealed the same organisms in a considerable percentage; it is therefore evident that these organisms are a part of the normal flora of the nasopharynx.

The removal of tonsils and adenoids reduces the bacteria of the nasopharynx, but considerable numbers still persist.

The adenoids, like the tonsils, are to be considered common foci where dangerous bacteria flourish and sources from which secondary infection may arise in the course of primary acute respiratory diseases and of chronic debilitating diseases.

EXPERIMENTAL LESIONS OF THE HYPOPHYSIAL REGION AND POLYURIA

McMicken Hanchett

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This work was begun for the purpose of determining experimentally the effect of intravenous injections of extract of the pituitary gland on the so-called polyuria of hypophysial origin. Before it had proceeded far, attention was attracted to certain striking variations from the generally accepted ideas concerning the production of polyuria of this type, and it seemed wise to investigate the means of producing it.

Dogs were used in all the experiments. Ether was used as the anesthetic and during the operation was administered by the intratracheal method. The gland was exposed by the buccal (transpharyngeal) route, first described accurately and used successfully by Aschner. In each case the normal urine excretion for 24 hours was measured as a preoperative control.

Synopsis of work:

1. Stimulation of the anterior and posterior lobes of the hypophysis: (*a*) varying degrees of heat; (1) heated rod; (2) paraffin; (*b*) trauma-pinching and pulling with tissue forceps; (*c*) cone-shaped plug of beeswax pushed into opening in bone; (*d*) induced current—electrical.

2. Herniation of gland through dural opening.

3. Traction on base of brain with as little trauma to the gland as possible.

4. Effect of pituitary extract, epinephrin and thyroid extract on polyuria.

Stimulation of the Anterior and Posterior Lobes of the Hypophysis with Heated Rod.—In this group 10 animals were used. After exposing the hypophysis, the gland was stimulated by traumatizing it with a metal rod of varying temperatures. The local effect, observed postmortem, varied from a moderate hyperemia of the anterior and posterior lobes to complete destruction of the gland. In only one instance was a polyuria of any considerable extent observed.

For 9 animals of this group the average 24-hour urine measured 210 c c and 204 c c for the 2 days immediately preceding the operation, and 220 c c, 214 c c, 224 c c, 286 c c, 250 c c, 180 c c, 260 c c and 200 c c for the successive days after operation.

In dog 2 there was a marked polyuria. The daily preoperative urinary excretion was 200 c c. The stimulation consisted in trauma with a rod heated to "blackhot" point, that is, the point at which the rod appears black after cherry red has faded. The rod was 3 mm. in diameter and was simply brought in contact with the structures at the bottom of the opening after the dura had been incised. At this stage in our work our landmarks were not as thoroughly impressed on us as they later were, and we were not able to locate the hypophysis definitely. During the first 24 hours practically no urine was voided. In the second 24 hours the quantity was 650 c c, and during the third 24 hours the amount increased to 1,500 c c. At this time the dog appeared to be very sick; scarcely able to stand. It was killed at the end of the third 24 hours. At postmortem examination it was found that our opening through the sphenoid bone was so far posterior that the hypophysis had not been exposed and that our stimulation had been applied to the base of the brain posterior to the hypophysis, the region of the corpora mamillaria.

Stimulation with Heated Paraffin.—In dogs 14, 37 and 39, paraffin heated to 70 degrees, 110 degrees and 130 degrees C. was poured into the cavity in the sphenoid bone without otherwise disturbing the gland. In dog 37 the dura was not incised. In no instance was there any change in the amount of urine excreted.

Mechanical Trauma Pinching and Pulling with Tissue Forceps.—In dogs 10, 11 and 21 the gland was traumatized by pinching and pulling on the anterior and posterior lobes with tissue forceps. On the 2 days preceding the operation the average urinary output was 150 c c in 24 hours. During the 24-hour period immediately after operation the average rose to 297 c c, after which it gradually fell until it reached 180 c c at the end of the fourth 24-hour period after operation.

Cone-Shaped Plug of Beeswax Pushed Into Opening in Sphenoid.—In dog 71a a cone-shaped plug of beeswax, approximately 1 cm. in diameter at the base and 1 cm. long, was forced into the opening in the sphenoid against the hypophysis. The gland was tipped slightly forward so that the plug impinged on both the anterior and posterior lobes. The preoperative excretion had been averaging 250 c c to 300 c c daily. The postoperative excretion was slightly less, being 150 c c to 250 c c daily. After 10 days of observation, the dog was apparently in normal physical condition and was used for other experimental work.

Induced Electrical Current.—The gland was stimulated by means of an induced current in dogs 58, 63, 66, 69a and 70a. In each instance there was an increase in the daily amount of urine. This was most marked in dog 63. During the 2 days preceding the operation the urine excreted in 24 hours measured 300 c c. Following electrical stimulation the amount increased to 1,400 c c in the first 24 hours, 3,800 c c in the second 24 hours and 4,200 c c during the third 24 hours. This polyuria lasted for 6 days, but as the urinary output was modified by other experimental work for which this animal was used, the remaining period will be discussed in detail later.

Herniation of the Gland Through the Dural Opening.—In dog 15 the sphenoid bone was much wider than is usual, and the surrounding venous sinuses were correspondingly formed in a larger circle. This made wider incision of the dura possible. When this step in the operation was performed, the gland herniated through the opening, forced through by a gush of cerebrospinal fluid. The degree of protrusion of the gland and the amount of spinal fluid were greatly in excess of anything previously noted. No manipulation was necessary to bring the gland well into view. A small portion of the anterior lobe was removed and the operation stopped. The dog was in excellent condition at the close of the operation. The urinary output during the 3 days previous to operation was 160 c c per 24 hours. This increased to 2,360 c c during the first 24 hours and to 3,680 c c during the second 24 hours following operation. It then fell to 2,140 c c in the third 24 hours. The dog was in excellent condition but was killed at this time in order that the tissue might be studied during active polyuria.

Dog 28 was operated on in the usual manner, and in this instance also the gland was forced through the dural opening by cerebral pressure. This herniation was not so marked as in the former case. Slight traction was made on the stalk, but an effort was made to avoid injury to the gland. The urine voided during the 2 days preceding operation measured 90 c c and 100 c c. During the first postoperative 24 hours 900 c c were passed. The quantity decreased to 200 c c during the second 24 hours. At this time this animal was in such bad condition that it was released from its cage. It died the following day. Postmortem examination showed no evidence of meningitis. The cause of death was bronchopneumonia. On the basis of these two observations, a group of 20 dogs was operated.

Traction on Base of Brain with as Little Injury to the Gland as Possible.—In these animals an effort was made to avoid trauma to the gland itself, while making traction on the stalk and its attachment to the floor of the third ventricle. The traction was made by introducing behind the gland a pair of dental cotton-holding forceps, the points of which extended forward beneath the pars nervosa. The stalk was grasped as gently as possible and the traction made through it on its attachment.

The complete result of this entire group may be briefly summarized as follows: average preoperative excretion in 24 hours, 150 c c; postoperative excretion per 24 hours, first—955 c c, second—960 c c, third—865 c c, fourth—700 c c, fifth—700 c c, sixth—500 c c, and seventh—190 c c.

The most marked polyuria of this group occurred in dog 55. The output increased from 200 c c on the days preceding operation to 4,000 c c during the second 24 hours after operation. This dog was allowed to live 6 days and was in good condition when killed. Postmortem examination showed a hemorrhage into the third ventricle. The hypophysis showed no gross changes other than the plastic exudate filling the defect in the sphenoid and covering the anterior lobe of the gland.

It will be noted that the entire number of the dogs in this group were not allowed to survive the full length of 7 days. It had been noted in our work, as in that of others, that a polyuria induced by stimulation in the region of the hypophysis was almost invariably a transitory condition, and its duration and the typical curve had been frequently described. Therefore, after the highest point in excretion had been reached, or at least such a point as could be definitely regarded as a polyuria, many animals were used for supplementary experiments. Some were killed to secure tissue at the height of urinary excretion for cytological study. Others were used to observe the effect of pituitrin and epinephrin on polyuria produced by stimulation in the region of the hypophysis.

Effect of Pituitary Extract.—Dogs 55, 56, 59a, 63 and 64 were each given M XV of pituitary extract (P. D.) in the femoral vein. In every instance there was a rapid drop in the curve of urinary excretion in the 24 hours following the injection. In 4 cases there was a secondary rise in the curve of the excretory rate followed by a more gradual decline.

Effect of Epinephrin.—Epinephrin was used in animals 67, 68, 69, 69a and 70. Doses of MV, M VIII and M X were injected into the femoral vein during active polyuria with no apparent change in the usual excretory curve.

In examining these results and the general problem of the etiology of polyuria of this type, one is at once brought face to face with the two schools of opinion:

1. Those who contend that the hypophysis, especially the pars intermedia, pars nervosa and infundibulum, is the important factor in the regulation of urinary excretion.

2. Those who believe that polyuria when associated with pituitary disease is, to borrow an expressive phrase, a "neighborhood symptom."

The inaccessibility of the gland accounts in a large measure for this difference of opinion. It is difficult even by microscopic examination to determine just what injury was done to the gland and to the neighboring base of the brain at the time of operation.

Every method of approach has its disadvantages. The two most generally used are the transtemporal (Paulesco) and the transsphenoidal (Aschner). The certainty of a definite amount of infection, the danger of hemorrhage and the inaccurate estimation of stimulation or trauma inflicted to the gland and adjacent structures are some of the objections to the method used in this work. On the other hand, we feel sure that the variable, unmeasured and unestimated traction on the attachment of the infundibulum to the floor of the third ventricle, when the gland is dislocated upward and laterally in order to expose the gland by the bitemporal (transtemporal) method, may be a very important factor in the production of the rather variable results obtained relative to polyuria.

As to the objections to the manner of approach used in this work, it may be said only one animal showed any evidence of infection other than the slight plastic exudate over the exposed portion of the anterior lobe. In this case a cotton pack was inserted to fill the opening in the sphenoid. In all others the opening was left wide open and thus maintained free drainage into the mouth. By care we were able to avoid hemorrhage.

While it is impossible to regulate accurately the degree and extent of the injury inflicted to the gland and its neighboring structures, we found no urinary increase of any consequence in any of the animals in which either the anterior or posterior lobes individually, or the entire gland, were stimulated by non-diffusible means, i.e., heat or mechanical trauma.

Stimulation of the hypophysis with an induced current produced polyuria. However, as an electrical stimulus may be transmitted over a considerable distance, it cannot be said that this trauma is limited to the gland itself, or that the resulting urinary increase is of hypophysial origin.

By traction on the stalk with an effort to avoid trauma to the gland itself, we were able to produce a polyuria regularly. We were able also to regulate roughly the degree of this increase, moderate or extreme, by modifying the amount of trauma (traction) exerted. Other animals operated, in which the same procedure was followed except for traction on the stalk, showed no or only slight polyuria.

It may also be said that in those experiments in which the hypophysis was mechanically stimulated, the injury to the gland was greater than that inflicted in the process of making traction on the stalk. In the case of the former group, the average daily pre-operative output of 150 c c was increased to 297 c c in the first twenty-four hours and then gradually decreased, reaching normal in four days. In the latter series the average daily pre-operative excretion of 150 c c was increased to 955 c c in the first twenty-four hours. It remained high and had not quite descended to the pre-operative level by the end of the seventh day.

The 3 outstanding experiments to which we would like to call special attention are those performed on animals 2, 15 and 55. In dog 2, the opening in the sphenoid was made so far posterior that the hypophysis was not exposed, and the stimulation (cauterization) was applied to the region of the corpora mamillaria. In dog 15, due to peculiar anatomic arrangements, the gland came through the dural incision with considerable force, followed by a larger amount of cerebrospinal fluid than had been usually observed. Except for these variations there was nothing done which had on previous occasions produced more than a negligible increase in the urinary excretion. In dog 55 there was found at postmortem examination a hemorrhage into the third ventricle. This animal was operated in the series in which traction was made on the stalk and its attachment to the base of the brain. The associated polyuria was the most marked in this group.

In these 3 animals we see: first, a conspicuous increase in the urinary output, and second, the presence of an additional etiologic factor. In dogs 2 and 55 there is gross evidence of injury to the base of the brain. In animal 15 the force with which the gland herniated through the dural opening may be considered to have produced trauma of the same sort but not appreciable microscopically. This is in accord with the results and conclusions of Camus and Roussy, which were published in 1914, but which did not come to our attention until after the completion of this work.

In the 6 dogs given intravenous injections of pituitary (P.D.) there was a definite transitory antidiuretic effect.

Epinephrin in 5 dogs and freshly prepared thyroid extract in 2 dogs produced no notable change in the quantitative urine in polyurias of this type

DISCUSSION

JOSEPH L. MILLER: This view is very interesting. I believe it was Kahler who injected into the anterior lobe silver nitrate and found that he could produce in animals a polyuria that lasted for several days. He also stated that drugs containing silver nitrate would do exactly the same thing in man—they would give a polyuria of several days' duration.

S. A. MATTHEWS: In regard to the question of polyuria induced by injury to the base of the brain, there seem to be two opinions; one, that it is due to injury in the region of the third ventricle, and the other that it is due to injury of the pituitary body.

Quite frequently, following the operation for extirpation of the pituitary body by the sphenoidal route in dogs, there is a polyuria of high degree, lasting from 24 to 72 hours. Out of about 100 operations on the pituitary gland (dogs) I have induced 3 cases of polyuria of a permanent character, lasting for from 6 to 8 weeks. The polyuria was of high degree; 5 to 6 liters (6 to 7 kilo dogs) in 24 hours and without sugar. The polyuria was accompanied by an intense polydipsia, both of which could be reduced to almost

normal by the administration of pituitary extract. In all of these animals the pituitary body was partially removed and some injury was inflicted in the region of the attachment of the infundibulum to the floor of the third ventricle.

As injuries in this region are frequently followed by polyuria (sometimes with glycosuria) without injury to the pituitary body, most observers consider the polyuria due to brain injury and not to injury of the pituitary gland.

A. J. Carlson: This communication brings to mind the fact that the correct observations of great men may at times lead us far astray by faulty reasoning. Schaefer years ago showed that intravenous injection of pituitary extract in dogs under anesthesia acted as a temporary diuretic. If this was a physiologic action the next step followed logically. Injury to the hypophysis may liberate too much of this renal hormone and we have the polyuria of diabetes insipidus. This view is still held by many clinicians. The theory is logical and based on a perfectly correct observation that in animals under anesthesia the intravenous injection of pituitary extract causes a temporary diuresis; but if the administration of pituitary extract is made without an anesthetic and one takes a 24-hour urine specimen, there is no diuresis. It is clear to us now that Schaefer's experiment did not permit the physiologic and clinical inferences drawn from it, and hence the complete "about face" in the rôle ascribed to the hypophysis in polyuria.

McMicken Hanchett (closing): I do not think I have anything to say except that this work was done at the suggestion of Dr. Dean Lewis on a fund which was furnished by Madam McCormick.

I am sorry that the time is so limited that we cannot enter into the discussion of the literature a little more fully. I agree with Camus and Roussy, who say that when it is impossible on gross pathologic grounds to explain any clinical phenomenon, there is a tendency to attribute it to some disturbance of the ductless glands.

NATHAN S. DAVIS, II
1858-1920

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1858-1920

Nathan Smith Davis, A.M., M.D., was born in Chicago, Sept. 5, 1858, being the younger of two sons of the distinguished physician and publicist, Nathan Smith Davis, M.D., LL.D., the founder of the American Medical Association and its early president, also the founder of its famous *Journal of the American Medical Association* and its first editor. The elder Davis was also one of the founders of the Chicago Medical College—now called Northwestern University Medical School.

The two sons of this famous American scientist followed in his footsteps and became physicians. The older, Dr. Frank Davis died shortly after entering practice, the younger, the subject of this biography, lived to carry out many of the ideals of his famous family and had a distinguished career in American medicine.

The writer knew Nathan S. Davis II as a boy, as a young man in his university and medical college course, and was afterward associated with him in college organization and general scientific societies—such organizations as the Illinois Microscopical Society and the Chicago Academy of Sciences. We spent much time together in amateur botanical and geological expeditions.

We also traveled and studied together in European universities. Dr. Davis was something of a naturalist. He was of a studious and book-loving temperament, but not the less a man of wide personal influence. He joined national and international scientific bodies. He traveled much to take part in the work of these associations, and his personal acquaintance was very wide among literary and scientific men. He was genial and magnetic rather than aggressive in his relations with people, and few who knew him well ever forgot his kindly, polished manners, his charm in speaking in public or private or the air of culture and a sort of old-school distinction that shone in his intercourse with others.

He resembled his famous father in features, having the broad, high forehead and deep orbits which made a face full of power and intellect. He was a handsomer man, of larger frame, than his father but less forceful—dynamic. Instead of the fiery eloquence and commanding leadership of the older Davis, he had rather the qualities of the pure

scientist, the research man, the nature lover, the post-naturalist—he was of the type of a Thoreau or a John Burroughs.

He shone in personal work among his colleagues. His fine, tall, handsome presence, his love of humanity and his mastery of the graces of intercourse made him greatly beloved by his students. He was none the less a good organizer and executive in university and public affairs.

While a student he won honors for scholarship. He lived in Evanston while attending the University there, and later entered the Medical School in Chicago. He stood number one in his class and at graduation was awarded the annual prize for highest scholarship with the A.M. and M.D. degrees in 1883.

His medical education was rounded by a postgraduate course at Vienna, where Dr. Frank Billings, Dr. George Isham, Dr. Elbert Wing, Dr. Frank Johnson and the writer, all young Chicago graduates, were more or less working as a group. Dr. Davis, with only American-taught French and German, rapidly perfected himself as a linguist, having a natural aptitude for languages, and before he left Europe had been accepted as assistant by Professor Arnold of Heidelberg, who usually declined to take non-German speaking men into his pathologic laboratory.

Continuing his career in Chicago, Dr. Davis was an able teacher in pathology at Northwestern University Medical School, holding the position of assistant professor in 1884. He was later appointed to the chair of practice of medicine. For a time he acted as secretary of the faculty and later succeeded Dr. Frank Johnson as dean of the medical department, holding that position for many years. He was also attending physician of Mercy and of Wesley hospitals, during these years, giving clinical lectures.

Dr. Davis gave considerable time and energy to national scientific bodies, being for many years first vice-president of the United States Pharmacopoeia Convention and a member of the Pan-American Medical Congress. In the Ninth International Medical Congress he was councilor of the Section on Pathology. At the same time he was active as a Fellow of the American Climatological Association, the American Tuberculosis Society, the Chicago Tuberculosis Institute and was one of the founders of the Chicago Institute of Medicine. He was also a Fellow of the American Medical Association and for a time was one of a group who gave valuable aid in the establishment of the *Journal*

of the American Medical Association, of which the Senior Davis was the founder and editor.

Dr. Davis was a trustee in many institutions; the Chicago Academy of Science, (chairman of the board); Northwestern University and the Young Men's Christian Association (vice-president). He was a member of numerous clubs and fraternities.

As a writer Dr. Davis' name was familiar in the scientific and medical journals of America. He was also the author of several books: "A Treatise of General Practice," made up of his lectures, and one on "Consumption—How to Live with It," "Diet in Health and Disease" and numerous monographs.

He had resided in California for nearly two years in an effort to regain declining health. For several years he had suffered from glandular enlargement which at times invaded the mediastinal spaces and which was believed to be lymphosarcoma. Although temporarily relieved by radiotherapy, recurrence finally became general, and he died Dec. 21, 1920, aged 62, at his home in Los Angeles.

E. WYLLYS ANDREWS

ANNOUNCEMENTS

The following have been elected fellows of the Institute:

Edmund Andrews
Wm. F. Peterson
Leon Bloch
S. A. Mathews

The next Pasteur Lecture will be given by Dr. Theobald Smith of Princeton, N. J., in October, 1921.

The following Fellows have been placed on the nonresident list:

Henry F. Helmholtz, removed to Rochester, Minn.
Richard S. Dewey, removed to California.
Fred Gaarde, removed to Rochester, Minn.
Philip Schuyler Doane, removed to California.

On April 29 a dinner was given by the Institute in honor of Sir William Herringham, chairman of the committee on medical education of the British Grants Committee and Vice Chancellor of the University of London, and Sir Walter Fletcher, secretary of the British Medical Research Council and Senior Demonstrator of Physiology, Cambridge University.

On June 20 a dinner was given by the Institute in honor of Dr. Carlos Chagas, Director Oswaldo Cruz Institute, Rio Janeiro, and Director of Public Health, Brazil. Dr. Chagas gave an illustrated lecture on American trypanosomiasis, a synopsis of which will appear in the next issue of the *Proceedings*. In responding to the introduction of the president of the Institute, Dr. Chagas said:

It is difficult for me to express as I wish my gratitude for the high honor that you have shown me in your country. You have received with the greatest kindness a modest Brazilian research worker whose scientific work is but enough to give him a modest name in his own country, and when compared with the great scientific work performed by the intelligent scientists of this country is as unknown. Fortunately, I understand your attitude, and in it I find once more the evidences for a high spirit of international cordiality; in it I recognize the superiority of a great people, always eager to stimulate and to promote scientific development in the farthest places of the world. From afar off in my own dear country we follow always wondering the great development of your scientific progress and applaud without limit memorable deeds that you add every day to your memorable history. In the field of science and especially in the scientific branches of medicine you reached very early the highest point of perfection. I have followed very closely your medical organization and in that I admire every day the power of your will and the efficiency of your culture. You have advanced very rapidly in your scientific evolution and you did it, gentlemen, dominated by that valuable sentiment of human solidarity that compels you to diffuse the benefits of your greatness to the other people of the world; that quickens you with the highest motives for promoting the happiness of life in all the world. Happy indeed is that country that is able to be a beautiful example of civilization and at the same time a great leader in altruism and moral greatness. Unfortunately, my dear friends, I do not speak your language with the perfection necessary to express to you exactly the gratitude I feel. It does not matter, however, because the language of the heart is always the same everywhere, and it is through the heart that I thank you very much.

SPIRIT BELIEF IN SCIENTIFIC GARB

JOSEPH JASTROW
University of Wisconsin
March 25, 1921

The belief in the action of spirit agencies is associated on the historical side with the foundation of modern spiritualism in the United States in 1848. This in turn is but a revival of an ancient belief which chanced to have a large following both in Europe and in this country. One source of the belief in spirit agencies arises from the folk-lore tradition which was responsible for the particular form which the manifestations assumed in the hands of the Fox children in 1848. While this historical aspect of the narrative must be considered, it is the main purpose to follow the attempt to support such beliefs by scientific evidence. Even as early as 1855 a scientific sponsor appeared in the person of Professor Robert Hare, who devised an apparatus by which the medium recorded messages through an indicator moving across an alphabet. The excitement of the movement brought forward from Faraday in England a device which showed that the moving of the table by way of raps and pushes was due to the involuntary efforts of the sitters. This little apparatus was actually used as a means of extending the cult, for this is the real origin of the "planchette."

The same well-known psychologic principle was set forth by Chevreuil in France, who referred the table-moving to the same force as moves the divining rod. So from the outset men of science have been prepared to leave their work to meet a public demand for a rational explanation of phenomena exciting public interest. But the testimony of the few scientific men who were prepared to believe in supernatural agencies had an enormous influence in spreading the belief in spirits. This is true particularly of the investigation of Sir William Crookes, and of the adherence of Alfred Russel Wallace to this belief

As spiritualism continued, new forms of manifestation were advanced, and from time to time men of science were called on to render a verdict as to their "validity," the usual alternative being that of supernormal or fraud. But the entire aspect of the problem was changed in 1882 by the foundation of the Society for Psychical Research, which attempted from the outset to undertake a strictly scientific investigation of all such phenomena. This approach changed

the emphasis from a belief in spirit agency to a possibility of the command of supernormal powers by specially endowed persons. The early adherence of this Society to the theory of "telepathy" set the current in the direction of all types of supernormal and occult beliefs. An important event was the report of the Seybert Commission in 1888. They examined a group of prominent spiritualist mediums in America, and without exception found all the manifestations due to gross fraud. It was probably through the influence of this report that the Fox sisters publicly confessed in 1888 that their raps, forty years earlier, had been produced by natural means.

Meanwhile a number of adherents to a belief in some form of supernormal agency had appeared, as shown in the writings of such men as Lodge, Richet, Lombroso, Flammarion, and others. While these accessions continued the possibility of maintaining a status for the supernormal, it can safely be said that the more recent studies have had the widest effect.

The main purpose of the present survey is accordingly to investigate the nature of the most recent evidence. It would be proper to begin with the investigation of Paladino which culminated in 1910 in the detailed exposure of her methods. While there was nothing novel or notable in her performances, it may safely be said that no one had accumulated such a large number of scientific sponsors for the "genuineness" of her mediumship. This alone accounted for her reputation. Her central performance consisted merely in "levitating" a table under conditions which presumably excluded fraud. It is this same phenomenon that in 1915 to 1918 was the subject of three books by Dr. Crawford of Belfast, Ireland. As an engineer, he explains the levitation by the principle of a "psychic cantilever." His books are full of tables and diagrams, pictures of apparatus and measurements, and therefore carry the air of scientific demonstration. When closely examined it appears that he is so convinced in advance that fraud is excluded that he gives this alternative the barest consideration, and is blind to the most obvious indications of natural (but fraudulent) operations. It is equally clear that his credulity increases as the investigations go on.

The largest center of the present interest in the occult is in Paris. There a considerable group of men are active in investigation and formulation, evidently prepossessed with occult ideas of spirit agencies. They have put forth elaborate theories centering about the phenomena of "materialization." They have founded an institution for such

studies, the president of which is Dr. Geley. The most elaborate publication is the book of Schrenk-Notzing, in German, and of Madam Bisson in French. The English translation from the German volume has recently appeared with additional material, and has precipitated a lively discussion. The evidence is minutely photographic, and presents the appearance of gauzy substances emerging from the mouth of the medium, and the further appearance of flat-like forms, which are disclosed behind a curtain under the control of the medium. The evidence rests, as in all such cases, on the exclusion of fraud; and this is totally unsatisfactory to a critical inquiry. The common feature in all such beliefs is the increasing credulity of the investigator, and their willingness to entertain theories which are extravagant to the degree of being pathologic.

While it is essential to the statement of the problem of spirit belief to understand the circumstances, historical and otherwise, under which such beliefs have arisen and have been promulgated, the fundamental interest lies in the nature of the mental processes concerned. It seems at first sight incredible that men trained to scientific thinking should be willing to conduct experiments which from the outset disregard the simplest scientific precautions. To the psychologist there can be only one interpretation; that of intense prepossession, however concealed, however subtle, however slight, and however much associated with clear, logical powers in other directions. The hypothesis of "logic tight compartments" or "reserved areas of conviction" seems necessary to explain the strange mingling of scientific argument and mathematical formula and observation after exact methods (which none-the-less violate the most elementary precautions against fraud) with a definite set toward an occult conclusion. The internal evidence of such an abnormal type of thinking is rarely absent. The hypothesis of the emergence from the body of the medium of a substance called "ectoplasm," which in turn is reabsorbed into the body of the medium at the close of the performance, is maintained as necessary, and to the authors plausible; and for no other reason than that they reject all other ways to account for the appearance presented. The total improbability of such an hypothesis seems hardly realized; it is easy to find collateral evidence that a mind capable of tolerating such an hypothesis (not to say cherishing and embracing) is also affected by attitudes of credulity and presuppositions of an unusual character. From the logical point of view, the fundamental interest lies in the alternative between fraud and extravagant hypotheses of this order. Naturally the demand

arises for the precise explanation of the appearances, nor has this obligation been shirked. The astounding documents of Dr. Schrenck-Notzing have been critically examined; it has been made clear that the true explanation of the gauzy substances lies in the fact that the medium is a regurgitant. The "materialized" substances are swallowed and brought up again as needed. The other "human form" flat phenomena are doubtless smuggled in when precautions are relaxed. However legitimate the demand for a concrete explanation, such a requirement can hardly be met when one considers the lack of control of conditions, and the fundamental fact that in all such performances the medium completely controls the time and manner of appearance. The very nature of a scientific experiment is that such control shall rest in the hands of the experimenter. The interest in the particular modes by which phenomena have been produced, which apparently suggest to those thus inclined to credit supernatural powers is, however, quite secondary to the psychologic problem of the attraction inherent in occult beliefs. It would appear that the "occult" must be accepted as a distinctive form of thinking which gives a peculiar satisfaction; in these days men recognize the need of a scientific sanction and thus invade the domain of science to find the support of scientific evidence. It is a tribute to the widespread authority of science that in the laboratory alone is it supposed that a convincing proof can be found. But what is actually presented is a travesty of science, a medley of a superficial scientific adherence associated with a fundamental unscientific credulity. It is as a remarkable example of such eccentric beliefs that the subject merits attention. It does so in addition through the historical fact that for one mind seeking proofs for this order, there are hundreds ready to accept the welcome conclusions on a totally different type of evidence. The fact that spiritualists and others committed to a belief in the occult look to the sponsors of so-called scientific experiment, places a responsibility on the true representatives of science to counteract such pernicious influences.

THE ETIOLOGY OF YELLOW FEVER

HIDEYO NOGUCHI, M.D.
Member of the Rockefeller Institute for Medical Research
April 25, 1921

The infectious nature of yellow fever was recognized by observers of the early eighteenth century, but the manner of its spread was not understood. Nott suspected mosquito transmission, and Finlay advanced the theory that Stegomyia fasciata was the mosquito which carried yellow fever from man to man. Finlay believed that a mosquito which had sucked the blood of a yellow fever patient was capable of transmitting the disease at once. Carter pointed out that there was always a period of about two weeks between the appearance of the first cases and the development of the secondary cases. This finding suggested a possible life cycle of the yellow fever virus in the mosquito body analogous to that of the malarial plasmodium. The final proof that the Stegomyia mosquito transmits yellow fever was given in 1899-1900 by the experiments in Havana of Reed, Carroll, Lazear, and Agramonte, and by the supplementary experiments of Guiteras and of Marchoux, Salimbeni and Simond. The Reed Commission confirmed the existence of the extrinsic incubation period (Carter) and the three days' duration of infectivity of yellow fever blood. The transmissibility of yellow fever to nonimmune individuals by direct injection of the infective blood was also established. The virus was found to be filtrable, and readily killed by heat at 50 C.; it was thought to be ultramicroscopic.

In 1918, a Yellow Fever Commission was sent by the International Health Board of the Rockefeller Foundation to Guayaquil, Ecuador, to study several problems in connection with yellow fever, among others, its transmissibility to animals, a point not sufficiently studied by previous investigators. It was found that guinea-pigs could be infected with the blood or emulsions of the organs from patients with yellow fever, and transmission of the disease to these animals was accomplished in 6 cases out of 27. The experimental disease in guinea-pigs, which followed an incubation period of 2-5 days, consisted of fever (1-3 days), jaundice, relative bradycardia, acute nephritis, and hemorrhages; death ensued within a few days. The fatty degeneration of the liver and kidneys was similar in distribution and extent to that found in human yellow fever tissues (Figs. 1 and 2), and hemorrhages into the gastro-intestinal tract were also constantly present. Recovery

EXPLANATION OF FIGURES

Fig. 1.—Fatty degeneration in the liver of a guinea-pig infected with Leptospira icteroides. Stained with scharlach R; × 110.

Fig. 2.—Fatty degeneration in the kidney of a guinea-pig infected with Leptospira icteroides. Stained with scharlach R; × 110.

from the experimental infection was found to confer on guinea-pigs a lasting immunity, just as does yellow fever in human beings. In the blood and organs of yellow fever patients and of the infected animals a minute organism was found, of which pure cultures were obtained; the organism passes through bacterial filters and is killed by a temperature of 50 C. Marmosets and young dogs could also be fatally infected, and in the latter the so-called black vomit was usually present at necropsy. Stegomyia mosquitoes became infective for normal guinea-pigs within a period of 8-12 days after sucking the blood of yellow fever patients or experimentally infected animals. The organism has received the name Leptospira icteroides.

Transmission of yellow fever from human beings to guinea-pigs and subsequent isolation of Leptospira icteroides has since been accomplished during several other epidemics: by Gastiaburu (1919) and by Noguchi and Kligler (1920) in Peru; by Noguchi and Kligler in Mérida, Mexico (1919-1920); by Perez-Grovas (1920) and Le Blanc (1921) in Veracruz. Stimson had made in 1907 an isolated observation on the presence of a spirochete in the kidney of a patient with yellow fever who died during the epidemic of 1905 in New Orleans; this organism has been found to be morphologically identical with Leptospira icteroides.

A positive Pfeiffer phenomenon with Leptospira icteroides has been obtained in most instances with the serums of convalescents from yellow fever. Injections of killed cultures of Leptospira icteroides confer on susceptible guinea-pigs and nonimmune human beings protection against the experimental infection and yellow fever, respectively, and the anti-icteroides serum checks the progress of the disease in animals or man when administered on or before the third day of illness.

From the foregoing findings the conclusion seems warranted that Leptospira icteroides is the etiologic agent of yellow fever.

AMERICAN TRYPANOSOMIASIS

STUDY OF THE PARASITE AND OF THE TRANSMITTING INSECT

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DEFINITION OF THE DISEASE AND A BRIEF HISTORY OF ITS DISCOVERY

American trypanosomiasis is a disease transmitted by hematophages of the genus Triatoma and is due to infection by Trypanosoma cruzi.

In the general symptomatology of the disease two distinct developmental phases are observable—the acute infection and the chronic. The acute infection is characterized from the parasitic point of view by the ease of recognition of the protozoon in the circulating blood in the form of flagellates, and from the point of view of symptomatology by the presence of signs of acute disease, especially of fever. In the chronic infection, on the contrary, the parasite disappears or diminishes to a considerable extent in the circulation and localizes itself in the tissues that make up the great organic systems.

The acute infection is found in the majority of cases in children during their first months, or, at most, during the first year of their life—a fact which bears on the epidemiologic conditions of the disease. In the zones infested by the triatome this insect is found in abundance in all human dwelling places, and the infecting index of the hematophages is very high. Therefore the newly born in such regoins soon become subject to inoculation by the parasite, and this confines the acute infections almost exclusively to early infancy. The acute phase of the disease is of short duartion, and as the symptoms that characterize it became attenuated and the fever disappears, the trypanosomes are no longer found in the circulating blood by direct examination and the patient passes to the chronic condition.

In the chronic phase the clinical signs are the expression of permanent alterations in the different systems and organs of the body. This aspect of the disease is independent of age, sex, race, or any other individual factor, and the patients of this category represent more or less remote infections.

The discovery of American trypanosomiasis was made under conditions which differ from the usual course of events in pathology. In this case, the knowledge of the parasite preceded that of the disease caused by it, and it was the data acquired in regard to the biology of the transmitting insect that indicated the investigations from which resulted the finding of a new nosographic entity. The first human case of infection by Trypanosoma cruzi was observed in the state of Minas Geraes in the interior of Brazil. We were there on a commission from the Oswaldo Cruz Institute carrying on an antimalaria campaign when we first came to know of the existence of a hematophage which was abundant in all of the houses. It was a blood sucker that lived in the cracks of the walls, from which it came out at night in the dark to feed on the blood of the people. During the day the insect remained in its usual hiding place; when the lights were extinguished, however, and when the people had gone to bed, the hematophage came to attack them in order to provide its own nutrition.

We examined samples of the insect and found in its digestive tubes flagellates with the morphology of Crithidia, and foreseeing the possibility of transmitting to vertebrates the parasites observed in the insect, we sent several hematophages to our master, Oswaldo Cruz, who fed them on monkeys of the genus Callithrix. One of these, fifteen or twenty days after contact with the insect, presented signs of disease, among which an acute keratitis was prominent. By examination of the blood of this animal we discovered the presence of a trypanosome which later experiments showed to be transmitted by the hematophage found in the human residences. We then inoculated the flagellates from the intestine of the insect into guinea-pigs and other laboratory animals and with complete constancy reproduced infections with a parasite identical to that observed in the monkey that served for the first experiment. In this way it was amply proved that the forms of flagellates first found in the hematophage represented developmental phases of a trypanosome of vertebrates.

With the object of finding the habitual host of the parasite, new investigations were undertaken in the regions where the transmitting hematophage had been found. As already stated, the hematophage had as its habitual habitat human residences, and this gave valuable orientation to our studies and early indicated the probable site of the animal parasitized by the trypanosome. The first work on the subject gave us an initial result, the finding of the parasite in the peripheral blood of

cats in houses infested by the parasite; furthermore, we observed in the persons living in those houses symptoms of a disease which in its complex defied any diagnostic interpretation, and seemed to indicate the existence of a new disease not included in the nosographic picture. These were the points of view that led us to more persistent search, seeing that the individuals were in a diseased condition. The examinations of chronic, apyretic patients were always negative; the occurrence, however, of acute febrile infection in a child of three months facilitated the work and cleared up the obscure facts. In the peripheral blood of this little patient, whose sickness had existed for a few days, there was found by direct examination a large number of trypanosome of a morphology identical to that inoculated by the hematophage into monkeys and to that transmitted to various laboratory animals by inocluations with material from the digestive tube of the insect. Thus there was demonstrated the existence of a new human trypanosomiasis, the later study of which showed pathologic aspects of the highest interest from the point of view of general pathology, and especially, of the pathologic physiology of some of the principal organs.

STUDY OF THE PARASITE

The Parasite in the Peripheral Blood of Man.—Trypanosoma cruzi, the agent of this new disease, is found in the peripheral blood of the patient only in the initial phase of the infection. When the acute symptoms have passed and the fever has diminished or disappeared, the trypanosomes localize themselves in the tissues of the organs, and this renders difficult the parasitologic proof, which at times can only be accomplished in the necropsies. Various observations of acute cases teach us that the presence of the parasite in the blood is always of short duration, on the average from 10 to 20 days, and the cases are rare in which one can find the trypanosome by direct examination of the circulating blood after a month of the disease. The morphology of this trypanosome is sufficiently striking to make it easily distinguishable from any of the other species of the same genus: the best specific characteristic is the size and position of the blepharoplast, which is larger here than in any other known trypanosomes and situated exactly at the posterior extremity of the parasite or very near to it. In the peripheral blood of man and also in that of other susceptible animals there are observed two distinct morphologic aspects of the parasite: in one of them the trypanosome has a general thread-like form and, what

is most characteristic, shows in blood smears stained by Giemsa's method an elongated nucleus in the form of a rod situated longitudinally; in the other aspect the parasite moves more slowly, in movements that are serpiginous rather than progressive, and presents a broader protoplasm and a nucleus of elliptical form, situated more or less in the central zone of the parasite.

We interpret the two morphologic types of the trypanosome found in the peripheral blood as a sexual dualism of the parasite, the thin form representing the male trypanosome and the broad form the female trypanosome. And, furthermore, this duality of sexes is well shown in the fecundation which occurs in the midgut of the triatome, where the trypanosome of the thin form attaches itself to the other, which previously assumes the rounded form. This phenomenon of fecundation, which is of such great interest in the biology of the trypanosomes, was chanced upon recently in its initial phase. Further investigations have completely elucidated the evolution of the parasite in the organ of the transmitting insect. Moreover, in the very structure of the two forms of the trypanosome and in the biologic conditions of each of them, sexual dualism was already indicated; the thin form, much richer in chromatin, of a more delicate structure, with more rapid movements, was characterized as a male organism, and the other form, broader, with less abundant chromatin and slow movements, presents the conditions of the other sex.

The Parasite in the Tissues of Man. Principal Organs and Systems in Which the Parasite Is Localized.—In the human organism and in that of all the susceptible vertebrates, the Trypanosoma cruzi evolves in two successive phases which take place in the circulating blood and in the interior of the tissues. Contrary to what is true for the other species of the genus trypanosoma, binary division in the blood is not observed in Trypanosoma cruzi, but its multiplication takes place within the tissues. In the initial phases of the infection in the acute cases of the disease and in any period in the chronic cases, the necropsies reveal abundance of the parasites in certain systems which constitute the seats of predilection of the parasite. Here the trypanosome presents itself in the form of rounded or pyriform corpuscles, destitute of flagellum and furnished with a central nucleus and blepharoplast, the latter situated near the nucleus or at the periphery. It is in this form that the parasite increases in number by successive binary divisions, from which result parasitic agglomerations, at times formed of numerous

units. These rounded leishmaniform corpuscles develop into the form of the typical trypanosome, furnished with complete flagellar apparatus, and then leave the tissues and return to the circulation. It is in this way that the numerical increase of the flagellates in the blood takes place in the recent infections, that is, in the acute cases of the disease. In the chronic forms, as the trypanosomes go from the tissues to the circulating blood, they are there destroyed on account of phenomena of relative blood immunity consequent on the long duration of the infective process. It is only by admitting this immunity that we can understand the absence of flagellates from the circulation of chronic patients in whose tissues the necropsy examination has demonstrated the presence of numerous parasites.

If the infection lasts for many years, as is amply proved, and if the aflagellate forms of the tissues evolve into the typical flagellates that return to the blood, how is this absence of the trypanosome from the blood in old infections to be explained? Only the hypothesis of a relative blood immunity can explain this fact, which has been repeatedly observed in the parasitic aspect of this trypanosome.

Although it may be found in nearly all of the tissues of the organism of vertebrates, the systems most frequently parasitized are the muscular —the smooth as well as the striated fibers—the nervous, and various glandular organs. The striated muscles in man and laboratory animals constitute the constant seat of localization of the trypanosome, which is there observed in agglomerations of numerous leishmaniform corpuscles. The same is true of organs of smooth muscle fibers. However, it is in the heart that the parasite is found especially, and there it is within the cardiac fiber proper, which is invaded and occupied by it in its entire length and breadth. In this way the cardiac fiber becomes transformed into a simple sheath of the parasite, which is completely contained in the space limited by the outer membrane of the fiber. When the latter ruptures, the protozoa fall into the interstitial tissue of the organ. Throughout the entire thickness of the myocardium parasitized heart fibers are found, and in any regoin of the organ histologic sections show cardiac fibers invaded by the protozoon, some of them with only a few corpuscles and others filled with them. Only the muscle is affected; as yet parasites have not been observed in the endocardium, the pericardium, or in the valves. In man and the animals susceptible of infection the heart is the constant seat of the protozoon. From the early stages of the disease on, the

necropsy examinations reveal an abundance of trypanosomes in the myocardium. And in the chronic cases, in infection acquired a long time previously, the same finding is revealed by the necropsies. We will see the importance of this localization of the protozoon when we study the pathologic processes and the general symptomatology of the trypanosomiasis.

The nervous system is another frequent seat of localization of Trypanosoma cruzi. Here the parasite conceals itself in the beginning in the plasma of the neuroglia cell, multiplies in the form of aflagellated corpuscles, destroys the cell, and continuing to increase in numbers, forms parasitic agglomerations within the nerve substance proper which are identical to those observed in the myocardium. Thus there are formed parasitic foci diffused throughout all the central nervous system with localization in the gray matter as well as in all the regions of the brain and the spinal cord. These parasitic foci of the nervous system bear no relation to the vascular system; they are observed in all the regions, even in the depths of the nervous matter, without anatomic dependence on the blood vessels. From this phase of the localization of the parasite in the nervous system result differential pathologic characteristics between the trypanosomiasis and syphilis, the spirochete of which, in its first sites in the nervous system, is subordinate to the distribution of the vascular system. In acute cases in man the trypanosome has been observed in the nervous system in various necropsies. From the localizations of the trypanosome in the nervous system in the acute infections there results, as we shall see, a condition of extreme seriousness, which is expressed by phenomena of acute meningo-encephalitis with rapid termination in death.

In man the general pathologic processes of the disease are directly related to the localizations of the protozoon in the various organs and systems.

Transmission of the Trypanosoma Cruzi to Animals.—Trypanosoma cruzi is transmissible to various laboratory animals. This is advantageous in the parasitic diagnosis of the disease and in the biologic study of the protozoon. Of the animals used in experimental work the guinea-pig, the dog, and the cat present the greatest susceptibility to the infection. The rabbit is less susceptible, and in it the infections are always relatively small. Adult dogs and cats are also more resistant, and in them the flagellates in the blood are always small in number. The resistance of white rats to this species of trypanosome

is notable, and in them the inoculation is often unsuccessful even when it comes directly from the transmitting insect. In the young guinea-pig, dog, and cat the infection reaches a notable intensity after some passages of the parasite through individuals of the same species; in the first inoculation, however, whatever the source of the parasite, the number of flagellates in the blood always remains small.

Cycle of the Parasite in the Insect Transmitter.—After biting man or any other animal that has parasites in the circulating blood, the insect transmitter becomes infective for new vertebrates after the lapse of a period which is not yet determined to its minimum limit. The infective property being once acquired, the hematophage preserves it for a long time, perhaps during its whole life, and even throughout the developmental metamorphoses that it undergoes. The period during which the infective property acquired by the triatome persists has not yet been determined with great exactness; we believe, however, that it lasts indefinitely, in view of the continuity of multiplication of the protozoon in the digestive tube of the insect.

The first phase of exogenous development of the trypanosome occurs in the quilific part of the midgut of the triatome where the flagellated forms, filled with the blood ingested, undergo the morphologic mutations that we will presently describe in detail.

In the intestiniform portion of the midgut, twenty-five hours after the infecting bite, are found numerous parasites, the majority of them having the structure of flagellates of the genus Crithidia. They remain in this portion of the digestive tube for an indefinite time, always increasing in number by binary multiplication, especially when the insect is regularly fed with vertebrate blood. The flagellates here show a great variety of aspects; however, the elongated forms predominate with the central nucleus and blepharosplast situated laterally and in front of the nucleus, in relation to the anterior extremity. Such parasitic forms are very motile and easily recognizable either in the examination of material withdrawn from the intestine or in the feces that are passed spontaneously, in which the crithidias are observed in abundance. These crithidia forms are observed with absolute constancy in all the insects fed on vertebrates with parasites in the blood; however, they do not constitute the last developmental stage of the trypanosome in the digestive tube of the hematophage. Indeed, beside crithidias there are observed later parasites with the typical morphology of trypanosomes, in which the blepharoplast is situated behind the

central nucleus relatively to the free flagellum. In these trypanosomes the nucleus is very characteristic and shows itself as a rod of chromatin situated in the central part of the plasm. They are very characteristic parasitic forms with narrower plasm than that of the crithidia, with serpiginous movements easily recognizable in the feces of the insect amid the crithidiaform flagellates.

We must emphasize the inconstancy of the appearance of the latter flagellates in the hematophages fed on infected vertebrates. While the parasites with the aspect of crithidia are always observed when the insect ingests contaminated blood, the trypanosome forms appear in a less regular manner, which makes us admit a determinism, not yet established, for the occurrence of this developmental phase of the protozoon in the insect transmitter.

To explain this duality of appearance of the flagellate in the intestine of the triatome, we admit the hypothesis of two developmental forms of the parasite. In one of them the trypanosome undergoes morphologic mutations identical to those found in artificial culture mediums, which consist of simple processes of division of the plasm without any process of initial fecundation. From this evolution there result as a final stage the crithidiform parasites which represent in some way the return of the trypanosome to its primitive larval condition. The other developmental form would represent the true biologic cycle of the trypanosome in the organism of the transmitter. Here there would be, as an initial phenomenon, a process of fecundation in the midgut of the insect between flagellated forms coming from the blood of the vertebrate. From this fecundation there would result parasitic forms whose state of complete development is represented by the trypanosomes found in the hind-gut. If this were so, the diversity of aspects of the flagellates in the hind part of the digestive tube of the hematophage would be explained: on the occurrence of an initial phenomenon of fecundation, which would depend on special conditions of the trypanosome in the blood of the vertebrate, the final stage of the development would be represented by flagellates with the morphology of trypanosomes; in the absence of this sexual phenomenon the parasites would reach the final stage of crithidias and would remain in it in the intestine of the insect. Direct observation does not yet authorize us to consider this doctrine as definite, but only to offer it under the reserves of a simple hypothesis. We have already in recent work shown the first phase of fecundation of the trypanosome in the

midgut of the triatome, and we hope in later work to clear up the development of the parasite in the organism of the transmitter.

The evolution of Trypanosoma cruzi here described was studied in adult insects born and reared in the laboratory and infected from man or animals with parasites in the circulating blood. Identical appearances, however, are observed in the insects collected in the houses of the regions were trypanosomiasis is existent. The triatomes from the human residences in any stage of their development are usually infected, the index of infection of the insect varying with the endemic conditions of the disease. In the hematophages the parasitologic examination always shows a greater abundance of the flagellates in the hind-gut, where they are seen sometimes under the form of crithidias and sometimes under that of trypanosomes. The intensity of the infection is quite variable; in some hematophages the parasites are numerous in the hind-gut and in the feces passed naturally, while in other insects the number of flagellates is very small. The parasitic forms of the hind-gut do not constitute the last stage of evolution of the trypanosome in the transmitting insect. Aside from these, others of a characteristic aspect have been found in the salivary glands, and these represent the parasitic forms inoculable into the vertebrate. This discovery has been a difficult one and up to the present has been realized rarely; however, its importance is not less as being demonstrative of the exact mechanism of transmission of the parasite. In the salivary glands the parasite has been seen in the interstitial tissue between the glandular cells. Here it is elongated, with a rodlike nucleus placed longitudinally, with much smaller dimensions than the forms of the hind-gut, with which it cannot be confused. This is the final stage of the exogenous cycle of the parasite equivalent to the sporozoites of malaria and of other protozoa transmitted by hematophages.

STUDY OF THE TRANSMITTING INSECT

The transmitter of the American trypanosomiasis is Hemiptera heteroplero, of the family Reduviidae, and genus Triatoma. The first species recognized as a transmitter of the disease was Triatoma megista; aside from this, however, the other species of the same genus can carry out the transmission, as has been proved with regard to Triatoma sordida infestans, and geniculata. Triatoma megista is in our opinion the specific transmitter par excellence, that is, the one in whose organism the evolution of Trypanosoma cruzi is best accomplished.

Artificially fed and under the temperature conditions of the tropics, the evolution of the triatome from egg to imago takes a minimum period of two hundred and seventy-one days. Under natural conditions of life it may at most show slight variations attributable to accidents of nutrition of the insect. In the laboratory the triatome lives for several months, and we have already observed specimens, periodically fed and in full activity, that have lived one hundred and fifty days. As the hematophage can transmit the parasite in any of its three phases of larva, nymph, and winged insect, by adding together the duration of the three periods of life, we can estimate at approximately four hundred days the period during which a triatome may exercise its rôle as transmitter of the disease. This fact well exemplifies the epidemiologic importance of a single hematophage, which when once contaminated may be the propagator of the parasite for a long time, contrary to what is true for other insects that are transmitters of various pathogenic germs, whose life is usually of short duration, which restricts the epidemiologic importance of each of these hematophages.

MECHANISM OF THE INOCULATION OF THE TRYPANOSOME

Infection by Biting and Infection by Feces.—The natural process of the inoculation of Trypanosoma cruzi into the organism of the vertebrate is by the bite of the insect, as happens with the majority of the parasites transmitted by hematophages. The transmission by bites was demonstrated experimentally in the researches of Magarinos Torres, who protected himself from any cause of error, and accomplished the infection of various laboratory animals by allowing them to be bitten by the insect. In these experiments only the proboscis of the hematophage entered into contact with the vertebrate and all possibilities of transmission of the parasite by the feces or by any other means were avoided. In various laboratory experiments with insects collected in human residences and with others reared and infected in the laboratory, Magarinos Torres in an indisputable way demonstrated the transmission by the bite. Furthermore, the presence of the flagellate was already demonstrated in the salivary gland of the insect and this constitutes a decisive demonstration of the process of inoculation by biting. It is true that the search for the flagellates in the salivary glands has not given the constant results that would be desired; on the contrary, rarely have we succeeded in verifying that final

developmental stage of the protozoon in the organism of the transmitter. In spite of this it is not possible to admit doubts as to the natural process of the transmission of parasites, since in other protozoon infections and even in trypanosomiases, which are evidently inoculated by bites, it has not yet been possible to verify parasites in the salivary glands of the insect, and at times it is not even possible to recognize the organisms of inoculation. In the case of Trypanosoma cruzi, after the repeated experiments of Magarinos Torres, which were carried on with a technical rigor that completely excludes any other mechanism of transmission, the inoculation by the bite of the insect is amply demonstrated. However, is this the exclusive mechanism of inoculation of the parasite? Certainly not, for it has been amply proved that the feces of infected insects placed on the mucous membranes of susceptible animals constantly brings about the infection by the trypanosome.

As we have already said, the flagellate is observed in the feces of the triatome in the forms of crithidias and of typical trypanosomes. The subcutaneous inoculation of naturally passed feces determines the infection with certainty in the laboratory animals. These facts, allied with the inconstancy of obtaining infection by biting, have led some investigators to promulgate the idea that the natural transmission of Trypanosoma cruzi is accomplished by the feces and not by bites of the insect. According to Brumpt and Piraja de Silva the inoculation of the parasite would be accomplished as follows: the triatome deposits the feces on the skin of the individual and, on account of the itching caused by the bite, the individual scratches the region affected, so that the nails produce slight abrasions which form the points of entry of the parasite. The inoculation would be caused in this way or by direct defecation on the mucosae of the eyes or mouth. Brumpt, who has shown that Trypanosoma cruzi easily passes through the mucosae, wishes to make a general doctrine for others, or for all the trypanosomes, of the processes of inoculation by the skin and by the mucous membranes. On the other hand, he considers the transmission by biting either as not occurring or as only an accidental and exceptional factor. With regard to Trypanosoma cruzi the opinion of this notable investigator does not seem to us acceptable. In the first place, the inoculation by biting has been experimentally demonstrated as possible and the trypanosome has been observed in the salivary gland of the insect. Furthermore, it must be noted that the feces of the

hematophage when once passed undergo rapid drying which results in the death of the flagellates. This being so, the infection by the skin could only be accomplished on the hypothesis that the feces are deposited on a region of the cutaneous surface that has been previously excoriated. At any rate Brumpt by repeated experiments demonstrated the difficulty of the penetration of the flagellate through the intact skin even in newly born animals. As to the excoriations produced by the nails, it must be noted that the bite of the insect is painless and does not provoke any itching. Two chief facts constitute a decisive objection to Brumpt's doctrine with regard to Trypanosoma cruzi: rapid drying of the feces of the insect after being passed and difficulty of penetration of the parasite through the intact skin. This being so, the only process of transmission of the parasite remaining would be the penetration of the mucous membranes as a consequence of the accident of the defecations occurring directly on the ocular or buccal mucous membrane. We do not doubt this last occurrence, which has been well shown in the experiments of Brumpt and in others carried on later in our laboratory. But to consider this accidental mechanism of transmission of the parasite as the rule and to place on a lower plane the biologic process of the bite does not appear reasonable to us; the experiments of Torres have resolved the subject by demonstrating the infection of the vertebrate by the bite of the contaminated insect to be possible and frequent.

According to Brumpt, the infection of vertebrates by some species of trypanosomes transmitted by hematophages would be accomplished by the ingestion of the transmitting insect. In this way that investigator emphasizes the importance of the feces in the transmission of the trypanosome and later refers to the infection of the rats as due to the fact that these rodents eat the fleas or lick the hairs contaminated by their dejections. This doctrine would at once be inapplicable to the transmission of trypanosomiasis to the great mammals by the glossinas of the African continent. As a result of decisive experiments and observations we can express the firm opinion that the natural transmission of Trypanosoma cruzi is accomplished by the bite of the triatome. The feces may constitute an accidental factor in the transmission of the parasite when they are deposited directly on the mucous membranes; however, if the defecations of the insect take place on the intact skin the penetration of the parasite does not occur, principally on account of the death of the flagellates by the desiccation of the feces.

RESERVOIR OF THE PARASITE IN THE OUTER WORLD

Trypanosoma cruzi, first found in the digestive tube of Triatoma megista and in the blood of man and the cat, was later found in the intestine of another species of triatome, Triatoma geniculata. This hematophage, unlike the first, is almost exclusively of sylvan habits, living in holes in the ground which form a shelter for a vertebrate that is common in Brazil, the tatu or armadillo. In a manner similar to what happens in the case of the flagellate of Triatoma megista, the parasite found in the Triatoma geniculata represents developmental forms of a trpanosome whose vertebrate host is the armadillo. In the peripheral blood of Tatus novencinctus, captured in the holes where were collected infected Triatoma geniculata, we found trypanosomes with a morphology identical to that of man and which reproduced in guinea-pigs infections identical to those caused by the human parasite. On the other hand, what better identifies the species of trypanosome and establishes the exact nature of the infection of the armadillo is the fact that the inoculation of the parasites of the digestive tube of Triatoma geniculata, collected in nature, in all susceptible animals caused infections with trypanosomes identical with those found in the armadillo and in man, both in their morphology and in their biology. In this way the existence in the outer world of a vertebrate host of Trypanosoma cruzi was well established and also that of a specific transmitter of the parasite. Thus, beside a house infection this trypanosome causes a sylvan infection, there being naturally between the two the difference of the transmitting species. Later investigations have shown that besides Tatus novencinctus other species are parasitized by the same trypanosome, which is observed with frequency in Dorypus sexcinctus and Dorypus unicinctus. Furthermore, it has been fully demonstrated that the infected armadillos are not only those collected in the regions inhabited by man and near the human residences; species captured in distant and entirely uninhabited places also show the trypanosome. The great frequence of the parasite in the armadillos has also been demonstrated, and, in certain places, they show a high infective index.

These facts, together with the low position in biologic development of the Daripodidae, which probably preceded man in the regions in the interior of Brazil where trypanosomiasis is endemic, caused us to conclude that the armadillos represent the primitive host of Trypanosoma cruzi, which is at present a human parasite through biologic

adaptation which has been accomplished in the course of time. The armadillos still constitute a permanent reservoir of the trypanosome in the outer world, and this fact is of great epidemiologic importance for the following reasons: The trypanosome that infects the armadillo has as its specific transmitter among animals of the same species Triatoma geniculata, a hematophage now adapted to life in the holes of the armadillos; this triatome, however, accidentally frequents human residences where we sometimes find it, which makes possible the contagion of man by the trypanosome of the armadillo. This being so, the Triatoma geniculata which perpetuates the infection by Trypanosoma cruzi in the outer world may constitute the carrier of the disease from its sylvan condition to the houses where it is perpetuated by the transmitting action of Triatoma megista. Brumpt also had the opportunity to demonstrate the presence of Trypanosoma cruzi in the digestive tube of a new species of triatome discovered by him and called Triatoma chagasi. This hematophage has been found in holes frequented by armadillos and other mammals.

Brumpt offered the hypothesis that this triatome is the primitive transmitter of the trypanosome the specific host of which in the outer world is Cerodon rupestris; however, confirmation of Brumpt's doctrine has not resulted from the prolonged investigations of Magarinos Torres, the parasite never having been found in Cerodon rupestris.

This being so, we remain with the conviction that the primitive host of Trypanosoma cruzi is the armadillo, and this at present constitutes a reservoir of the parasite in the outer world.

CLINICAL ASPECT OF TRYPANOSOMIASIS

American trypanosomiasis is observed under two essential aspects: an acute infection and a chronic one. In the acute infection are included cases in the first phase of the disease presenting the initial symptomatology, in which the febrile reaction predominates. This condition of the disease is principally characterized by the presence of flagellates in the peripheral blood. The chronic infection includes the infected patients who have escaped death in the first phase of the disease and in whom are observed clinical syndromes, predominating on the side of certain apparatuses or organic systems, according to the localizations of the parasite and to the lesions occasioned by them.

I will discuss the acute infection in general outline. This is almost always observed in children during their first months or, at most,

within the first years of existence. Acute infections occur almost exclusively in infants on account of the domiciliary condition of the disease and the high infecting index of the hematophages in the human residences.

The child, as soon as it is born, becomes subject to the bites of the triatome and consequently to inoculation with the parasite; for this reason it becomes quickly infected. Does hereditary transmission of the parasite occur? As yet we are not in a position to give a definite solution to this point which is of great importance in the epidemiology of the disease; we believe, however, that the transmission of the disease by intrauterine contagion often occurs, in spite of the fact that we have not yet succeeded in obtaining unquestionable evidence of it. We think thus because otherwise many facts of common osbervation, such as the fact that individuals present evident symptoms of the disease without having experienced any former acute attacks, would be inexplicable. Considering the fact that trypanosomiasis in its pathogenesis presents an appreciable similarity to syphilis, it is not to be wondered at that in this point they also bear resemblances.

The duration of the course of the acute cases has varied in our observations between ten and thirty days. One of two events may then occur: either these cases terminate in death within a few days or they pass to the chronic form, with a course which is sometimes long, so that the infected person may reach an advanced age, although with appreciable anomalies in some organic systems.

In the acute form there is always a complex of pathognomonic symptoms that are absolutely constant and not confusable with other diseases. This is the general symptomatology of these cases: continuous fever persisting while flagellates exist in the peripheral blood, reaching a temperature in the more serious cases of 40 C., with slight morning remissions; spleen and liver always enlarged in volume; general glandular enlargement, the glands of the neck being appreciable in large numbers and those of all the peripheral plexuses being enlarged. Finally, as a more characteristic sign we must refer to the swollen face, so that the patient appears bloated; so peculiar to trypanosomiasis is this appearance that it constitutes one of the most certain symptoms for the diagnosis of the acute forms, raising the suspicion as to the nature of the infection even at a distance. This last sign, on which we must insist, is one of the most peculiar in trypanosomiasis; some days after the appearance of the febrile reaction

and after the child presents itself as a patient, the parents note the appearance of this tumefaction, which is most marked in the face and other regions of the body, this as a rule being the sign of disease that attracts most attention and leads them to seek the physician.

By clinical investigation it is easy to prove that this is not a case of renal edema but rather one of myxedematous infiltration, of generalized myxedema, and this is confirmed by the histologic examination of the subcutaneous cellular tissue in which the reactions of mucin are appreciable. Thus in the acute forms of trypanosomiasis one of the elements of myxedema is observed with extreme frequence, this being a fact which indicates a functional alteration of the thyroid gland in this initial phase of the infection. And the necropsies in cases of this nature, by showing the presence of the parasite and histopathologic processes in this gland, give a foundation for this symptom and make evident the attack of the parasite on the thyroid gland.

From the point of view of prognosis the cases of acute infection are divided into two groups: in one of them there are symptoms pointing to involvement of the nervous system, and the patients present appreciable signs of acute meningitis; and in the other such signs are not observed. In the first group of clinical cases the gravity is much greater and termination by death within a short time is the rule; and at necropsy marked lesions are found in the brain and meninges with localization of the parasite in the brain substance. The anatomopathologic signs are those of an acute meningo-encephalitis, and the parasitic foci may be observed in any part of the brain. In these clinical cases the greater abundance of the parasites in the peripheral blood should also be noted. On the other hand, in the acute cases without meningo-encephalic symptoms death is rarely observed, the patients usually passing to the chronic state.

Let us proceed to consider the principal aspects of the chronic infection. The predominance of some syndromes on account of the localization of the parasite in certain organs justifies us in admitting some principal clinical forms in the chronic infection; but we must state that between these forms there are no sharp limits, because in all there are some symptoms which are constantly present and constitute the essential characteristic of the disease. In some cases, however, the symptomatology is more accentuated in certain organic systems, and this gives a basis for the systematization of the disease into some

clinical groups in which certain functional changes predominate. We shall study the principal of these clinical aspects in a general way, it not being possible here to enter into minute descriptions.

CARDIAC FORM OF THE DISEASE

Among the most notable facts in the pathology of this disease are the localizations of the parasite in the cardiac muscle of man and laboratory animals, within the proper fiber of the myocardium. This being so, it can be understood that in the clinical expression of trypanosomiasis cardiac symptoms at times figure in a predominating way. The heart changes in this disease form one of its most curious aspects, and in them we find a great mass of facts that are of value in elucidating the points that are still obscure in cardiac pathology. This is true because, by the aid of the functional change which is appreciable by clinical methods, it is not difficult to verify the etiology and pathogenesis which are represented by the parasite in the myocardial cell and by the lesions determined by it in the whole muscle.

From the beginning of our clinical studies of the disease, our attention was attracted by the cardiac arrhythmia in young persons without any sign of generalized sclerosis, and without symptoms of any inflammatory process in the kidneys. The cases of this nature that came under our observation in a relatively short space of time and in a diffuse population were numerous. Certainly outside of the epidemiologic conditions of the regions in which we were studying, alterations of cardiac rhythm were never observed in so high a number in young people. In such patients there are always found other symptoms of infection; here, however, the changes in the circulatory apparatus predominate.

The first necropsies of the disease soon explained this fact of constant observation by demonstrating the parasite in the myocardium and the lesions there caused by it in acute and chronic cases of trypanosomiasis. In laboratory animals numerous experiments also indicated the predilection of the parasite for the cardiac fiber. Those properties of the cardiac muscle fiber that become principally affected are those of excitability and conductibility, according to numerous observations that we now have.

The alterations of excitability include extrasystoles which occur here with extreme frequency and under the most variable forms. There are seen characteristic extrasystoles of auricular origin and

others of ventricular origin. From the point of view of frequence of the extrasystole there are also presented the most varied appearances, as they occur either infrequently interspersed between the normal systoles, or repeated in each cardiac cycle, giving to the pulse the classic aspect of bigeminism. Many other aspects are here observed in which all the variations of cardiac rhythm may be characterized.

It is worthy of note that these alterations of rhythm are observed at any age, even in children of 6 and 8 years; and it should also be noted that, in spite of the abundance of parasites in the myocardium in the acute cases, in these there do not occur alterations of rhythm but rather a great insufficiency of the organ. We believe that such alterations depend on processes of diffuse myocarditis with interstitial sclerosis of the organ, an anatomic condition which is still absent in the early stages of the disease and only found in the chronic forms.

Next to the arrhythmia from extrasystoles attributable to disturbance of excitability, come in order of frequency the alterations in the conductibility of the myocardium. Here are observed all grades of disturbances of the function, from its initial decline to complete elimination in which the ventricular rhythm is independent of the rhythm of the auricle. In the initial depressions of the function it is curious to note the cases in which in the tracings from time to time an auricular systole is not transmitted to the ventricle, thus causing intermittent gaps in the radial pulse. In this way occur the numerous cases of relatively slow pulse that are observed in the zones of the trypanosomiasis with less than 60 radial pulsations per minute.

When the bundle of His is attacked, with profound disturbances of the conductibility of the muscle, there result cases of complete heart block, the true Stokes-Adams syndrome, in which there are not lacking the concomitant nervous disturbances. The number of patients already observed with this syndrome is high; and we can state that, in this particular, trypanosomiasis presents a pathologic condition that is peculiar to it, no other disease existing in which the slow pulse is observed with so great a frequence. Especially notable here is the observation of heart block even in children from 8 to 12 years of age.

Without doubt, the cardiac form represents one of the most curious clinical aspects of the new disease and also that of the greatest fatality in the chronic forms. Death caused by this diseased condition usually occurs from asystole due to progressive weakening of the heart. The patients then present generalized and progressive edema, visceral con gestion, and other symptoms that characterize cardiac asystole.

Another mode of death that is of great frequence in the zones infested by trypanosomiasis, is sudden death from cardiac syncope. This fact causes wonder in all those regions in which we have studied the disease; young persons relatively healthy die suddenly, sometimes while at work, without any recent symptoms that could make one foresee this event. The exact mechanism of this death has been the object of prolonged investigations in our studies, and it is possible to interpret the accident under two hypotheses: either they are cases of complete heart block, death occurring in the long pauses in the cardiac pulsations, or we are dealing with a phenomenon of auricular fibrillation, which is still poorly understood in man. Concerning this last hypothesis we have a curious observation, the report of which cannot be included within the limits of this summary description. Be that as it may, sudden death in trypanosomiasis is frequently observed and is associated with the profound changes of the myocardium caused by the localization of the parasite.

NERVOUS FORM

Histopathologic studies carried out in necropsies on the bodies of persons who had presented nervous symptoms simultaneously with other symptoms of the disease have shown localization of the parasites in the central nervous system and lesions caused by it there. It is impossible in this résumé to discuss the nervous form of the disease in its various and curious aspects, and I prefer to discuss interesting phases of the disease. From the beginning of our clinical studies we observed numerous cases in which organic affections of the nervous system coexisted with other signs of the disease.

The high coefficient of nervous syndromes in the zones of trypanosomiasis, the cases of paralysis, of aplasia, of idiocy, observed principally in children or in persons of retarded development soon formed one of our greatest clinical surprises, indicating at the same time the high pathogenic importance of the parasite, in case it would be possible to demonstrate it as the etiologic agent of such nervous changes. We were naturally led to the association of the nervous syndromes with trpanosomiasis by the existence of other clinical signs of trypanosomiasis in the patients referred to, and by the negative results of all investigations in which attempts were made to find another etiologic factor; a negative Wassermann reaction, absence of physical signs of syphilis—exact clinical studies all excluded the interference of the treponema of Schaudinn in such alterations.

The first necropsy on a child that had died with signs of acute meningo-encephalitis gave an anatomic base to our clinical observations and justified the creation of the nervous form of the disease. The principal anatomic characteristic of the localizations of the parasite in the central nervous system and of the lesions there produced is that they are in multiple foci, scattered in different zones of the brain, in the cortex, bulb, etc., and without any relation to the arterial system. This multiplicity of localizations is well expressed by the various forms in which the nervous syndrome presents itself in the clinical cases. Among the motor disturbances the type most frequently occurring is cerebral diplegia, in which, as a rule, the spasmodic phénomena predominate over the paralytic. However, such diplegias, which are generally consequent on infections acquired during early life, from the point of view of extension and intensity of the disease present great variations of aspect, from simple bilateral dysbasia expressive of anatomic scars consecutive on lesions of slight extent up to the forms of generalized rigidity, the true Little's syndrome.

In any of the nervous forms of the disease the historical data usually refer the beginning of the nervous changes to acute attacks, probably of meningo-encephalitis occurring in early life; however, we know of cases of primitive localization of the parasite in the brain, the disease proceeding from its beginning with a silent course without symptoms of an acute meningo-encephalitis.

The intelligence is always affected in the nervous forms of the disease, and intellectual deficiency is here observed from the most complete idiocy to the simple states of retardation, and there is no obligatory relation between the intensity of the motor disturbances and the degree of mental decadence. Many cases classifiable as complete idiocy present slight motor changes expressed simply by exaggeration of the tendon reflexes, dysbasia, etc.; on the contrary, there are cases of profound motor disturbances with relative preservation of the intelligence.

Alterations of speech are also not rare, and there are a large number of diplegics who show a total aphasia. While this, on the other hand, is almost always accompanied by motor disturbances, as times it constitutes the most salient manifestation in patients with slight alterations of motility. Generalized or partial convulsions are also frequently observed in the disease and express lesions of the cerebral cortex. They have been observed with all of the clinical

aspects of the nervous form of this disease. Suprabulbar paralysis has also often been observed in cases of diplegia, sometimes amplifying the nervous syndrome and sometimes constituting isolated paralytic manifestations in persons with other signs of the disease but with normal general motility and tendon reflexes. It is not difficult to understand the existence of these suprabulbar paralyses when we know of the diffusion and multiplicity of the parasitic foci in the neuraxis.

The results of trypanosomiasis on the nervous system having thus been described in a summary way, I shall refer in bare outline to some other aspects of the disease concerning which there still are certain objections, either relative to their association with the infection or to the method of interpreting their exact pathogenesis.

INFANTILISM

Cases of retarded growth with total arrest of physical development are frequent in the zones of trypanosomiasis. Many of the patients in this group represent classic types of myxedematous infantilism with evidence of hypofunction of the thyroid gland; others, however, are far from that type and do not show appreciable signs of hypothyroidism. Must we establish relations of cause and effect between this infantilism and infection by Trypanosoma cruzi? Certainly. In the first place, aside from arrest of development, other signs indicative of the disease are found in such patients. In some necropsies the parasite has been found in its seats of preferred localization. Aside from this, it must be emphasized that the parasite localizes itself in the essential endocrine organs and systems, such as the thyroid gland, the genital organs, the suprarenals, etc. Here it has localized itself and caused lesions that change the functional correlations between such systems or destroy the necessary antagonism. This being so, it would not be possible to deny the influence of such changes on the total physical development of the patient.

Nor is it to be wondered at that infantilism figures among the results of infection by Trypanosoma cruzi. The analogy for this aspect of the disease is found in syphilis, the pathology of which presents notable points of contact with that of trypanosomiasis. Does syphilis not include infantilism among its consequences? And why may this not also be the case with American trypanosomiasis, when the contagion in this disease may also take place during intrauterine life

or the infection may be acquired during the first months or even during the first days of existence? I have no doubt that in the zones of the "barbeiro" infantilism constitutes a result of the disease; investigations are in progress which may better elucidate this point.

ENDEMIC GOITER AND TRYPANOSOMIASIS

A point that is also debatable is what is said with regard to the relations, if there are any, between American trypanosomiasis and the goiter that is endemic in the regions where the disease exists. In rapid synthesis I shall give the reasons that cause us to consider the goiter endemic in the infested regions to be a result of infection by Trypanosoma cruzi.

One of the most salient clinical signs in the acute form of the disease is the mucoid infiltration of the subcutaneous tissue. This is a constant sign and indubitably expresses the interference of the thyroid gland in the pathologic condition. We must note that, in the large number of observations that we possess, we are treating of children who were formerly free from any of the signs of myxedema, this having appeared days after the beginning of the infection, that is, as an immediate consequence of it. Furthermore, in necropsies on acute cases the parasite has been observed in the thyroid gland, which forms another argument in favor of our opinion.

On the other hand, in numerous cases of goiter studied in the zones of the "barbeiro" the coexistence of symptoms of trypanosomiasis is constant, and if in many cases of the disease it is easy to verify absence of appreciable hypertrophy of the thyroid gland, it is difficult to verify the inverse condition.

The facts of the epidemiology and of the geopraphic distribution of the disease also give foundation for the same opinion. Thus it is that in the infested zones goiter is only found in persons who reside in houses where the transmitting insect is encountered; while the inhabitants of houses free from infestation by the hematophage, although under the same conditions of life, fed in the same way and drinking the same water, do not show lesions of the thyroid nor the effects of goiter. As to the geographic distribution of the disease and of endemic goiter in regions of the interior of Brazil, our observations superabundantly show the coexistence of goiter and the hematophage that transmits Trypanosoma cruzi, and as yet we have not been able to find any region infested by the triatome in which goiter does not exist.

It is true that the presence of goiter in some of the zones along the coast of the country in which the "barbairos" have not been found seems to contradict this doctrine; however, we must state that we have never affirmed that goiter is always a consequence of infection by the trypanosome, which would be absurd. We believe in the diversity of etiologic factors of struma, and even in our country we have the conviction of the diversity between the goiter observed in certain regions of the coast and that which constitutes the great endemics in the zones where the trypanosomiasis exists. To recapitulate our idea in this respect, we will say that we associate the endemic goiter observed in the regions of the interior of Brazil, which are infested by the transmitting triatome, with infection by Trypanosoma cruzi. We have strong arguments that lead us to think in this way; in spite of this, however, we do not consider this point definitely elucidated, and we believe necessary other investigations which we will take up in order to give our doctrine indisputable proof or to make it unsupportable.

THEORIES OF SUSCEPTIBILITY AND RESISTANCE IN RELATION TO METHODS OF ARTIFICIAL IMMUNIZATION

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> It is provided in the essence of things that from any fruition of success, no matter what, shall come forth something to make a greater struggle necessary.
> —Walt Whitman: "The Song of the Open Road."

The function of great men seems to be not only to bring revolutionary ideas and concepts into the world before they are due, but vigorously to maintain and defend them in a hostile environment. Many great ideas are launched but not developed and defended. The systems in vogue are either indifferent or hostile to them and the individual unable to meet indifference or hostility, hence they are lost for the time being. Pasteur not only brought forth ideas revolutionary to biologists, chemists, and physicians of his age, but he developed and perfected them and advanced them into practical life in the face of great opposition.

Medical science is particularly indebted to him for his pioneer work in the immunization of the body against infectious diseases. Since his time his fruitful ideas and achievements have given origin to two more or less commingling streams of scientific and practical endeavor; one devoted to the further development of methods of protective inoculation, the other to the elucidation and analysis of the complicated biologic machinery underlying acquired immunity.

Confronted with the fullness of knowledge brought to light by the generation since Pasteur's earlier work and set afloat on these two streams, the writer, who has worked through this past generation, realizes that there is a certain congestion and blockade which tends to leave us near some Tower of Babel. It seemed therefore worth while not so much to penetrate into the subject as to define it from the outside, to circumscribe it by a statement of accepted compelling facts based on general biologic concepts. I have therefore used few technical immunologic terms and given no references since the ideas will be found elsewhere if search is made for them.

BIOLOGIC ASPECTS OF SUSCEPTIBILITY AND RESISTANCE

In a recent paper I emphasized the fact that all parasites, from the ultramicroscopic to the larger worms, which go from host to host within the same species, must pass through some cycle which involves the critical phases of entry, multiplication, escape, and transit to another host. Each one of these phases is made up of series of minor stages following each other in definite succession. Every parasite has a cycle differing in major or minor details from every other parasite. The phases of these cycles are undoubtedly associated with physiologic and perhaps with morphologic changes in the parasites. The bacteria are unfortunately not susceptible to much analysis with our microscopes, but much has been suspected and written, as shown by the recent monographic compilation of F. Löhnis (1921). The discovery of a series of stages in the sporozoa, involving both vegetative and reproductive processes, makes it probable that the parasitic bacteria may not be without similar, even though very rudimentary phases. Interpretation of morphologic divergencies are at best difficult. The many explanations which the microgametocyte or the so-called flagellated organism of the malaria parasite passed through before its relation to the sexual cycle was made clear should suggest caution in sweeping aside the interpretation of active phases in favor of the well-worn one that they are involutions of bacteria. The many important observations on mutations, on the enzymes of bacteria, on sensitiveness to oxygen tension, and on the phenomenon of d'Herelle indicate that we have still much to learn of the manifold capacities of even the commoner bacteria.

The continued existence of the parasite presupposes escape sooner or later to a new host. This is accomplished by the localization of the parasite near convenient places of exit, chiefly on, or in, or under the skin, the mucous membranes of the respiratory, digestive and genital tracts, and the glands secreting outwards, such as the testicles and mammary gland. These conditions are fundamental, and I think will be accepted as real by all those who have given some attention to bacterial, protozoan, and higher parasites.

Besides the complete cycles of parasites there are many incomplete and aberrant cycles. They may be internally aberrant in so far as the parasite departs from the normal route through the host, or they may be externally aberrant when parasites belonging to one host get a partial foothold in another. There may be multiple or consecutive invasions into the same host. All these departures from the normal parasitic

cycle are responsible for a large part of the sum total of what we call disease. They complicate study and postpone solutions. They make moderate disease severe and fatal and interfere with both preventive and therapeutic measures.

The phase of the parasitic cycle which is significant to both parasite and host is the multiplication of the parasite in the tissues, or the vegetative stage. In this stage the parasite must injure tissues to a certain degree and in case there is more or less destruction of the progeny of the invading parasite foreign protein, toxins, enzymes and the like must be disposed of. The injury is quantitative and in all adjusted parasitisms multiplication is held in check or controlled by the host. The relation between the two is a flexible adjustment or truce, for the failure of self-protection on one side is identical with overactivity on the other.

The special relations existing between parasite and host have their roots in the distant past. In the formation of these relations both host and parasite had to give way. Natural selection had to eliminate from both before the existing arrangement came to a fair degree of stability. This mutual adaptation will explain the special group of parasites centered about each mammalian and avian host, to mention only species related to us and of economic importance. That relations between hosts and parasites should now and then be found to exist not explainable by natural selection and adaptation but due to accidental relationships need not surprise us.

The rapprochement between certain hosts and certain developing parasites implies an equal estrangement between other hosts and these same parasites, often terminating in the formation of species and even genera of parasites from the same ancestral stock by adaptation to different hosts. This adaptation to one host leads to the immunologic concepts of susceptibility and immunity. A given host which becomes the habitat of a certain parasite is susceptible. Another host owing to physiologic differences becomes immune to the same parasite.

The foregoing inevitably leads to the doctrine that the specialization of parasites and their host restrictions are due as much to the host as to original endowments of the ancestors of the parasites themselves. Specificity of a parasite is, in part at least, the stamp put on it by the host If this is true it follows that in the normal host, independent of any earlier invasion of his parasites, certain functions are correlated with those of the parasites he as a species possesses. In the language of

Ehrlich, we might say that there are certain nutriceptors in the host correlated with certain activities of the parasite. This would define for us what is meant by susceptibility. It is a positive rather than a negative attitude, at least in the early stages of the parasitic cycle. This definition of susceptibility leads directly to a definition of natural immunity, that condition of the body which is unfavorable to the multiplication of certain parasitic organisms. In some cases it reveals differences between closely related species or even races; between house mice and field mice, chickens and pigeons, white mice and Japanese waltzing mice, not to mention the many differences existing between man and the domestic animals with reference to their parasite equipment.

If our definition of susceptibility approximates the truth, natural immunity may be defined as a lack of those physiologic states or functions possessed by the susceptible animal which favor the parasite. The immune species or race is without that which reacts in the presence of the parasite and causes enough disturbance to furnish a nidus for multiplication and such food material as is set free by the reaction or disturbance of function. This reaction may involve both primary toxic and anaphylactic phenomena, or at least certain modifications of them. This definition is in harmony with the generally accepted doctrine that both natural immunity and susceptibility are histogenic; that immunity, however, which is simply based on the fact that some one link in the chain of parasitism is defective, such as the capacity to enter the host, is not fundamental, for the link may at any time be supplied and thus create susceptibility. Immunity to be basal must fail to supply that link which promotes the multiplication of the parasite in the host, for in the end this stage is most dangerous to the host and important in providing for the continued existence of the parasite

There is one type of more or less complete resistance which manifests itself where diseases have been prevalent or endemic over long periods of time. Even in small groups, herds, or flocks, a disease sooner or later plays itself out through a slowly rising resistance of the group, provided fresh individuals and races of virus from other groups are not brought in. This kind of resistance may be a high degree of acquired immunity, due to vicarious vaccination from early life on with small doses, possibly with the cooperation of a passive immunity developed during fetal life or the lactation period, or it may be a gradual decline of reactivity to the presence of the living parasite,

or what is still more probable, both processes may be at work until the second is completed and natural immunity finally established. Natural immunity thus may grow out of susceptibility by a gradual loss of those normal physiologic reactions to invasion which favor the parasite. Natural immunity like natural susceptibility exists only with reference to specific parasites. The host species immune to one parasite may be highly vulnerable to another closely related to the former. Parasites of one host may be as vulnerable in another host as are free living organisms. The parasitic acquisition is specific with reference to one host, partially so with reference to some others, and negative with reference to still others.

If we now consider those processes which stand out as of primary significance to both host and parasite—the multiplication, survival, and discharge of the latter—are we in a position to circumscribe these phenomena and thereby limit the field of inquiry? That they are different for every group of parasites may be assumed, but how superficial or deep the differences are cannot be told until the behavior of every group is studied individually. For this study the past generation has furnished much material, but it remains to fit it to each parasite. The forces of the host directed against the parasite are presumably stimulated by the metabolic and growth activities of the latter, and among these we must look for the antigens that count. The antigens locked up in the parasites and available only after the parasites are dead and disintegrating cannot be of any importance, if normal forces must first kill to make antigens available. The sufficiency of resistance rests in the destruction of the parasites, and if this is done before certain antibodies can be mobilized and overproduced they cannot be essential to the host's protection.

There are probably a variety of ways in which multiplication is suppressed. It is conceivable that the interference with a single function may be sufficient. The host probably accomplishes this suppression either by direct destruction as when the cholera vibrio is introduced into the immunized guinea-pig, by interfering with the normal metabolism as in the antiblastic immunity of Ascoli, Dochez and Avery, or by inducing the formation of some protective envelope around the parasite. In any case the host is protected when, and as long as, multiplication is suppressed. The mere presence of a few parasites is of little or no significance.

In the highly adapted parasites the multiplication is more or less definitely measured out to the parasite by a delicate balancing of forces. As a rule, the induced disturbance or disease is moderate, nonfatal, unless complicated by other parasitic invasions. There are, to be sure, always hypersusceptible hosts to be weeded out—to restore the host-parasite equilibrium.

In the partially adapted and aberrant parasites, the relation between host and invaders is less clear. In this class belong all experimentally induced diseases when another host is substituted for the natural one. The body probably brings into play whatever forces are available, i. e., whatever forces are stimulated by the particular parasite involved.

Since the discovery of the antitoxins, the so-called antibodies have been in the forefront of all theories bearing on host-parasite relations. These bodies, which appear in quantity usually some time after the invasion, are supposed to suppress the multiplication of parasites in some way. But there is ample evidence that some inhibiting forces are active from the start. They may be considered normal antiforeign forces, and it simplifies our theories considerably if we assume that they are also the immune bodies stimulated later to overproduction by the products resulting from the multiplication of the parasite. If the immune bodies are not normally present, eventually overproduced bodies, then we must assume the existence of normal forces active at the outset and producing much the same results until the immune bodies are mobilized. There are, however, physical and chemical conditions in the tissues not antigenic in character which may oppose multiplication either wholly or partially. If wholly, the host must be regarded as naturally immune.

We may then presuppose a steady opposition to multiplication from the start on the part of the host, which is countered by the parasite and which eventually gives way or suppresses multiplication completely after a certain period. The sources of the specific-antibodies have been referred to the organs producing lymphoid, polymorphonuclear and other cell elements, such as the lymph nodes, bone marrow, and spleen. It is not improbable that antibodies may be products of actively secretory cell tissue as well. These substances are carried by the blood, and there is ample evidence of the antiparasitic activities of this fluid. Free living, saprophytic forms are destroyed by it, and parasitic forms, even though not necessarily destroyed by it, avoid the blood except when passively carried by it. In disease they crawl along lymph channels, serous membranes, enter joints, or find shelter in

injuries. They even inhabit cells for protection. They appear last in the blood in moribund conditions, and their capacity to multiply in it is the function to be suppressed first in artificial immunization.

On the part of the invading organisms there must be some factors which neutralize the normal, antiforeign activities of the host. To some organisms the start is given by an injury which interferes with the normal circulation locally and thus prevents free access of protective forces. Injury probably plays a much larger rôle in the beginnings of infection than is currently granted. It may be exceedingly slight for some infections. Among certain parasites, the injury is inflicted by the parasite itself. In the evolution of the parasitic stage, the parasite to make its way must have possessed certain aggressive destructive functions which are gradually pared down to the required parasitic level. Such agencies to be effective must act in the immediate environment of the parasite to create the needed locus for multiplication.

We have then the metabolism of the parasite and its products in opposition to those of the host. Where do these two groups of forces articulate? What are the substances given off by the parasite which are acted on or neutralized by the normal antiforeign forces, and which among them represent the so-called antigens? What are the normal forces at work not belonging to the antibodies? Evidently a variety of conditions may exist. I wish to call attention to but one. In the evolution of certain parasites the functions of the latter may have developed in such a way as to approach the host's functions more and more, antagonistic processes dropping out. Granted that host reactions are proportional to the alien character of the substances to be digested and assimilated, the approach of the metabolic processes of the parasite to those of the host might eliminate hostile reactions more and more while reducing correspondingly the injurious effects of parasitism on the host. The most advanced parasitism may be conceived as consisting in the direct utilization of host substances as food. That such adaptation is possible is in accord with the marked differences in the behavior of what we call distinctly animal and vegetable parasites. The former, even the very minute, tend to produce prolonged associations with the host, often lasting years, with relatively little destruction of tissues except those cells and structures in which they may develop. The latter are responsible for the acute invasions and more or less sharp decisions in which host or parasite or both may perish. Certain diseases, like tuberculosis, appear to negative this hypothesis as being

chronic processes, but the local processes are actually acute and destructive, and the apparent chronicity of the disease is due to the interval elapsing between the series of acute reactions following invasion of new territory.

Illustrations of possible relationships between parasite and host, such as this, suggest the importance of studying special parasitisms since the fundamental processes are to all appearances highly modified and diversified from group to group. We cannot be certain that a given process favors the host or the parasite, since even primarily protective functions may have been modified through natural selection in the presence of parasites into neutral or even parasite-favoring operations. So the process of phagocytosis may be protective, indifferent, or even against the host. In the hatching of the embryo in the digestive tract the parasite makes use of the antiforeign digestive juices of the host to escape from its shell.

Returning to the aggressive and repressive processes active in infectious disease, we may ask whether these are operating simultaneously throughout the disease. On the surface it seems as if most diseases could be divided into a period of infection representing the multiplication of the microbe and a period of subsidence in which certain antibodies appear in quantity. It is, however, probable that the aggressive and defensive activities go together and that what we actually see is a resultant in which one or the other temporarily predominates. If repressive forces are not active from the start, it is difficult to account for the slow multiplication of the parasite and its rapid increase toward the death of the host when the latter has been overpowered. In a few diseases only does the body act like a culture tube. In such cases multiplication in the blood goes on from the beginning. In the rest it is slow, retarded, and gives evidence of steady opposition on the part of the host tissues.

In the attempt to illustrate the supposed diversity in the mechanisms involving the multiplication, inhibition, and discharge of the parasite, we are confronted by the incomplete knowledge of the life history of any parasite or infectious agent within the host. If I, nevertheless, attempt such illustration it is more in the spirit of suggesting problems than of solving them by speculation.

Taking as our first illustration the diphtheria bacillus, we may assume in view of the large amount of work done that this organism's chief weapon is the toxin. When this is neutralized it is checked. The

toxin through injury provides a nidus for multiplication. When the antitoxin prevents further injury its food supply is cut off. Having no other means of resisting the host tissues, it remains a surface parasite.

The group coming next in order includes the so-called septic diseases. If we except anthrax, the organisms of septic diseases are as a rule mucous membrane parasites of some host, and the septic effect is usually due to transfer to a fresh susceptible host. In this group the evidence points to a normal antibody to the aggressive, injurious product of the parasite in the blood. The organism gains a foothold through some trauma, and this protects its nidus until it gains the upper hand or is suppressed by the mobilization of more antibodies. Some support is given to this view by Kraus' successful treatment of anthrax with normal cattle serum. The promptness with which antibodies can be set in motion determines whether the local focus is suppressed or widens out into septicemia.

A somewhat higher stage of parasitism is presented by the typhoid and paratyphoid bacilli. While the typhoid bacillus appears to be linked to the human species, the paratyphoid group is represented by a number of serologic varieties whose definite host relations, beyond that of *B. suipestifer* or the hog cholera bacillus, are in doubt. The typhoid bacillus is of special theoretical interest because of the general agreement that a vaccine of killed bacilli establishes a definite resistance to the disease. When we try to formulate what we know of the cycle of this bacillus we find little, if anything, precise in the clinical and pathologic treatises. A priori, two cycles are possible: a simple cycle of limited multiplication in the small intestines, and a cycle beginning with prompt invasion and multiplication in lymphatic structures, discharge through lesions of the same into the intestinal tract. Or the bacilli may primarily multiply in the intestines, and thence, through lesions established there or produced by other parasites, enter the tissues and continue multiplication for a time.

These cycles if adhered to would lead to two types of virulence, one approaching cholera or dysentery, the other producing focal lesions in various tissues and organs. Clinical and epidemiologic data do not exclude the existence of such types. In effect it is probable that the virulence of typhoid bacilli oscillates between the two extremes, now one, now the other predominating, according to environmental and host conditions. If the bacilli multiply at the outset in the small

intestines, the infection of the environment would take place early. If discharge depends on ulceration, it would be late. The first type is adapted for extensive infection, at a given time, of water supplies, milk, etc., the second only for immediate contact in unsanitary environment because of the lateness of the discharge and the scarcity of the bacteria given off. The second type would be more virulent, more invasive, and more dangerous to life, and vaccination would appear less successful.

There is little in the immunologic work on record to enable us to interpret the precise relation of the typhoid bacillus to the tissues of the susceptible host. There is an endothelial cell reaction pointed out by Mallory which may also be detected in the lesions of some types of paratyphoid bacilli. The multiplication is a focal one. If more highly specialized types should appear, the focal reaction would approximate that of tuberculosis. Tubercle-like foci sometimes appear in smaller experimental animals. Resistance to the invasive paratyphoid races, like *B. suipestifer*, is brought about only after prolonged effort at vaccination.

A parasite standing still higher in its specialized habits is the tubercle bacillus. This organism has been persistently studied for many years, its operation is relatively slow, drawn out as it were, and its activities written in the tissues as are fossil remains in the rocks.

Three races of bacilli, bovine, human, and avian, produce tubercles of similar structure in their respective hosts, but each is practically powerless, with certain exceptions, to do this in the two other hosts. The simplest explanation of this specificity is that each host species has added or subtracted or modified something in the tubercle bacillus or its progenitors to adjust it to its own conditions. Each race in multiplying attracts and stimulates reproduction of endothelial cells. It modifies them to a certain degree. What is the significance of the tubercle? Is it a nest established by the parasite for multiplication, or is it a defensive shutting in by the host? If the tubercle did not form, what would happen to the bacillus? Can it multiply freely in the sinuses of the lymph node where deposited? If we examine the process more closely we shall probably come to the following tentative explanation: The entering tubercle bacillus is carried in some phagocyte into the regional lymph node. Here the bacillus multiplies in the phagocyte, rather than free in the lymph channels. It may be that multiplication in the lymph currents is unfavorable owing to some nor-

mal repressive substance in blood and lymph. At the beginning of multiplication, chemotactic substances draw about the bacilli the endothelial elements and perhaps stimulate them and fixed cells to multiply. If the endothelial cells become densely crowded, central necrosis sets in, probably aided by specific products of the bacillus. Rapid necrosis and softening favors extension of the disease by dissemination and new tubercle production elsewhere. The tubercle may thus be said to be protective both to the host and parasite. But the fate of both host and parasite probably depends on what goes on in it, how quickly it is formed, how large it grows, how fragile or resistant the elements.

The metabolic products given off in the tubercle stimulate the production of antibodies. When the bacillus passes out to form a second crop of tubercles, these are less likely to become necrotic owing to an increasing resistance. The bacillus to escape finally to another host must lodge in organs secreting or opening outward. Here partly or wholly released from the control of the circulatory antibodies some races, such as saprophytes, multiply abundantly in mucus, as in many cases of human pulmonary tuberculosis, others rarely, as in the bovine disease in which they are simply thrown out with the disintegrated tubercle masses.

In the attempt to influence the course of such a disease it has been difficult to find a point of attack. Evidently either actual infection with living attenuated bacilli or those measures which raise the normal physiologic capacities of the host to a higher level are theoretically promising, unless analysis goes further and discovers what goes on in the tubercle, what substances pass in and out to influence the tissue reactions, and what significance is to be attached to the vigor or vitality of the cells forming the tubercle.

When we pass to the highly specialized parasites which produce the so-called eruptive diseases of man and animals, limited usually to a single host species, so little is known of the intimate relation of the parasites to the host tissues that illustrations are not available. On the other hand, the highly specialized protozoan parasites whose relations to the host tissues are fairly well known cause little reaction in their environment and complete their cycle with trifling opposition on the part of the host. The mechanisms which on the one hand prevent the host from destroying or suppressing the parasite and on the other check the overmultiplication of the parasite in the vegetative phases,

show their existence only occasionally, as it were, by their deficiency. From this group much will be learned in the future that will aid in elucidating the more violent reactions in bacterial infections.

PRACTICAL ASPECTS OF ARTIFICIAL IMMUNIZATION

Perhaps one of the first problems to be forced on the investigator who has successfully identified and cultivated the micro-organism of a given infectious disease is that of providing some preventive treatment, usually in the form of a vaccine. Giving an active immunity and being easily and cheaply provided in large quantities, vaccines always have appealed to those in preventive work, and they will doubtless continue to do so. Before discussing the bearing of theories of susceptibility on vaccinal procedures, it will therefore be advisable to pass in hurried review our practical acquisitions in protective inoculation.

Up to Jenner's time, near the end of the eighteenth century, mankind had learned that lives may be saved by exposing individuals by cohabitation with those having a disease, or by rubbing into mucous membranes the infectious secretions and discharges and thereby producing less severe, less fatal attacks. This mode of protection reached its culmination in smallpox inoculation, which was practiced so extensively in the eighteenth century. At its close Jenner published his brilliant and epoch-making observations on cowpox and demonstrated its protective action against smallpox. The principle involved in cowpox as a vaccine is perhaps the most subtle and elusive of all those which come into play in vaccination. It means the irreversible modification of a virus without any loss of propagative vigor when grafted on another species. Jenner regarded cowpox as coming from an eruptive disease of the horse called "grease." Later it was regarded as a direct derivative of smallpox, rubbed into the cow's udder by the milker. Quite recently de Jong described an eruptive disease among horses which produced on calves and infants typical vaccinia vesicles. If we add to these observations the rare but well supported production of cowpox experimentally with smallpox virus, we are at present justified in assuming that both cowpox and horsepox are producible from smallpox. Such an inference would probably leave all the controversialists of the nineteenth century, were they still alive, amply satisfied. But it would be ungrateful and unfair to recall that small but faithful, persistent, hard-working group of medical men simply as controversialists, who during the latter third of the nineteenth century

gave up their lives to the study of smallpox vaccination, introduced the newer ideas from the youthful bacteriology, and protected the method from the attacks of numerous hostile groups whose activities are not yet spent.

In historical order, the next fundamental addition to the principles and technic of protective vaccination was Pasteur's production of so-called attenuated anthrax virus by exposing actively growing cultures to a temperature slightly above that of the human and animal body for a certain number of days. The longer the exposure the weaker the resulting virulence. This lowered virulence was impressed on the entire progeny of the exposed culture. By this means viruses fatal to mice only, to mice and guinea-pigs only, and to mice, guinea-pigs and rabbits, were produced.

The permanent reduction of virulence by heat acting on a growing culture has not been successful with other strains of pathogenic bacteria. The anthrax vaccine thus far stands alone. Before and during Pasteur's work, Toussaint, Chauveau, and others had experimented with heat in the mitigation of anthrax virus. They did not, however, modify their virus, but simply weakened or killed it. During this active period, Chauveau experimented extensively with compressed oxygen and Pasteur's pupils with antiseptics.

Next in order came the demonstration in 1886 by D. E. Salmon and the writer that cultures of certain types of bacteria killed by heat may confer immunity. This demonstration in particular covered only the paratyphoid group.

In his prolonged investigations of rabies and the final production of a successful vaccine, Pasteur made use of the principle underlying the modification of smallpox into cowpox. He had somewhat earlier applied this principle in the making of a vaccine for a bacterial disease of swine, known as rouget, Rotlauf, and swine erysipelas. The bacillus of this disease was passed through a series of pigeons to increase its virulence toward swine and through a series of rabbits to reduce it. The rabbit virus was to be used as a vaccine, the pigeon virus to test the vaccine's efficiency. Owing to the confusion caused by the coexistence of several infectious swine diseases, not recognized at that time, this vaccine could not get a fair trial.

In the vaccination against rabies the virus had been so modified by a long series of passages through rabbits that it may be said to be relatively harmless to man. Added to the precautions represented by

this modification is the serial injection of the mitigated virus dried for different periods, the vaccine to be first applied being killed by the drying and thus producing a preliminary immunity similar to that obtained from heated virus.

Following the differentiation of mammalian tubercle bacilli into human and bovine races, Behring and Koch undertook to use the human type to protect cattle from their own type of bacillus. This procedure led to a certain degree of resistance in cattle, but its full value has never been gaged by exhaustive experiments. One of the reasons for abandoning this procedure was the survival of the human bacillus and its appearance in certain rare cases in the milk of cows vaccinated when very young. This incidental result is of no significance to the cow, but the specific use of milk for man would require preliminary pasteurization if this mode of immunization were used. This method of using a closely related living strain of virus on animals relatively immune to it as a vaccine may yet play a prominent part in the struggle against disease both of man and his valuable animals.

One other important factor has been added to those enumerated, namely, the use of specific immune serum with the vaccine. The many animal plagues of diverse character threatening to reduce our valuable food-producing animals to a low level of physical efficiency, if not to wipe them out altogether in time, have tended to stimulate research in the direction of protective vaccines. The first to use immune serum with virus as a vaccine was R. Koch and his coworkers in investigations of rinderpest in South Africa. The immune serum was injected simultaneously with fully virulent blood and tended to restrain the otherwise dangerous vaccine and make its effect similar to that of an attenuated virus.

This so-called simultaneous vaccine was subsequently used with success by de Schweinitz and Dorset in the immunization of swine against the filtrable virus of hog cholera. In this procedure the virus is simply a passage virus maintained in swine and capable, by itself, of setting up severe and fatal disease. Similarly, the attenuated anthrax vaccine of Pasteur has been reinforced by the simultaneous use of a specific immune serum. With this combination Sobernheim was able to use a stronger vaccine than is safe if the culture alone is used.

The next step in the use of serums was the direct mixing of vaccine and specific immune serum. It had been shown that if diphtheria toxin and antitoxin are mixed in such proportions, that a local lesion following

the subcutaneous injection is just avoided, an active immunity is nevertheless induced. If the mixture contains enough toxin to produce a local lesion, the active immunity is increased. On the other hand, if the toxin in the mixture is gradually reduced below the neutral point, active immunity is reduced to the vanishing point. By using the passively immunized offspring of guinea-pigs treated with toxin-antitoxin mixtures, I was able to demonstrate the existence of active immunity in the mother as long as she could be kept alive. In 1913 Behring suggested the use of such mixtures for the active immunization of children. Since then William H. Park has made this field his own and made this method of vaccination a practical success. The mixing of living or dead cultures of bacteria with the specific immune serums induced by them in horses has been extensively used by commercial organizations preparing biologic products in the production of so-called sensitized vaccines.

Returning to the earliest practices, the induction of disease by direct inoculation or cohabitation to prevent a more severe spontaneous attack, I wish to call attention to certain practices which involve the introduction of the unmodified virus. In contagious pleuropneumonia of cattle, it has become customary to practice protective inoculation by inserting the fresh virus into the subcutis of the tail. Owing to local conditions and the protective agencies at work to keep the virus from reaching the lungs, the process set up where the virus is deposited leads to immunity.

In another bovine disease, universally prevalent today, in which the placenta of the pregnant cow is the locus of multiplication of the virus, the introduction of the unmitigated virus will produce a high degree of protection provided the virus does not escape into the utero-chorionic space during pregnancy. Strains of this bacillus attenuated merely by artificial growth produce a relatively high resistance if the culture is introduced before gestation begins. The udder in many cases becomes a secondary immunizing focus and tends to prevent the escape of bacteria into the pregnant uterus.

Over and above the use of vaccines to protect against certain dreaded plagues, there have come into use vaccines to mitigate or suppress infectious processes actually under way in the body. Most of the processes to be influenced by this method are chronic parasitisms of skin and mucous membranes.

This brief historical retrospect is chiefly impressive by reason of the variety of methods in use. No two are precisely alike. They are manifestly reflections of differences in the diseases to be combated and may be grouped under three heads.

1. Artificial cultures of living micro-organisms, chiefly bacteria, attenuated in virulence by heat, age, medium, etc., or killed by heat.

2. Virus modified and mitigated by passages through some alien species.

3. Virus presumably maintained as nearly normal as possible by passages through the normal host species and, in the vaccinated animal, kept within control by simultaneous injection of specific antiserums or by introduction into a tissue or region at a distance from the seat of the disease.

In the endeavor on the one hand to illuminate the natural processes of disease from the point of vantage gained by experimental immunization and mass vaccination, and on the other to improve the latter through a rational analysis of the natural process, it is important to bear in mind several limiting conditions.

1. All forces appearing in the course of disease and recovery from infection are present in the normal animal, even though in a relatively inactive state and are capable of being stimulated even to overproduction. The disease or vaccination process does not add anything to the individual, but simply starts a given machinery and mobilizes its products. The individual through vaccination does not acquire any greater capacity for production and mobilization of protective forces and it is well known that to certain individuals the benefit of vaccination is brief and transitory. In practice such individuals would be vaccinated oftener than the average. The maximum possibilities of immunization are, however, definitely fixed by the species characters, as laboratory tests on animals well show.

2. We are in the habit of dealing with parasitism through its clinical manifestations. These are only what may be compared to the visible spectrum. To the infra-red portion may be likened the incubation period, to the continued parasitism after recovery the ultraviolet end, or we may compare it with the frequency curve in which the ordinates represent the clinical disturbances. These begin imperceptibly at one end, increase, and then fade away at the other. Through vaccination the visible spectrum may be eliminated, but not the infra-red or even the ultraviolet end. Thus in typhoid, vaccination may suppress the

tissue invasion but not any intestinal multiplication if the bacillus is sufficiently saprophytic to undergo this process. In smallpox the primary lesion, probably in the respiratory tract, may develop, but its dissemination and final multiplication in the skin may be suppressed. In tuberculosis the primary lesion may start but get no further; or, to describe these occurrences in a more general way, it may be said that if mobilization of the immune bodies is dependent on stimuli, something must happen before they appear. This happening may be the development of some primary lesion after invasion.

Vaccination, then, may be more accurately defined as dividing the impact of a diseases into several milder ones. If the natural resistance to a given infection is already high, vaccination may indeed suppress all further manifestations. There is a similarity between vaccination and the Danysz phenomenon. This tells us that it takes less diphtheria toxin added in successive partial doses to neutralize a given dose of antitoxin than when the latter is neutralized with one dose.

3. Vaccination is administered in the same degree to the normally susceptible, the highly resistant, and the highly susceptible. Are we to assume that the same procedure brings these three classes to the same level of resistance? Naturally not. In the highly susceptible, the natural attack may be so softened that what might have been fatal becomes a more or less regular attack with recovery. If we inoculate a series of mice with a virulent paratyphoid and observe that some die and others either recover or fail to show signs of disease, the difference between these is not due to the inoculation but to the make-up of the mouse. If we inoculate again later those that failed to die, they simply will have a less difficult process to undergo. In certain diseases, the evolution may be postponed by artificial immunization. It will enable the animal, highly susceptible to certain paratyphoid strains, to resist apparently one or a limited number of fatal doses. If such animals are kept long enough after a period of apparent immunity, a slower type of disease develops with greater prominence of the tissue reaction. Eventually death ensues. Tuberculosis may be thus postponed by vaccination and the type of disease slightly altered.

4. In the diseases against which vaccination of one kind or another has been practiced on large numbers, viruses of such high virulence appear from time to time that the usual acquired protection is broken through.

In the host-parasite relationship the identification and correlation of the factors concerned in favoring and suppressing multiplication should be followed by an inquiry as to which of them and to what degree they may be stimulated to increased activity by so-called antigens. Unless they are stimulated to overproduction, some name other than antibodies is called for, and the use of the name antibodies restricted to those which appear in decidedly increased quantities toward the termination of the parasite cycle. From the accumulated literature on immunity we may postulate, I think, that some of the immune forces, notably the antitoxins, are easily stimulated into increased activity, others with difficulty and slowly. There may be others which increase only with the age of the host. Against the rapidly multiplying septic organisms the reaction with immune forces is equally rapid; against others, such as tuberculosis and leprosy, it is increased with difficulty. There may be parasites against which the normal protective forces cannot be increased.

Of the three groups of vaccines mentioned in the foregoing, it is the first made up of living or dead, easily cultivable bacteria, which has absorbed most attention since it presents a large field for exploitation and promises a considerable number of cheap, easily produced vaccines. In this group the micro-organism under artificial cultivation, either under conditions favoring a maximum multiplication or under constraint on account of physical conditions, gradually loses in part what we call virulence, i. e., its capacity to multiply in its established hosts. This partial loss may be due to various changes, in particular the disappearance of those characters which give the organism its distinctive parasitic qualities, aggressive or self-protective. The function of such a vaccine is to multiply just enough to give an impulse to the specific antibacterial forces before being suppressed and destroyed. The easy preparation of different anthrax vaccines by different periods of exposure to a dysgenetic temperature, leading to such vaccines as mouse anthrax, guinea-pig anthrax, rabbit and sheep anthrax, has given to the whole procedure an air of simplicity which it really lacks. Epoch-making discoveries usually happen through a combination of industry, accident, and the rare capacity to seize on the fleeting apparition of success. So it was with anthrax in the hands of Pasteur. No other vaccine has given such definite results.

Between highly attenuated living bacteria and those killed by the lowest sterilizing temperature there is only a slight difference. It is

quite possible that living vaccines can be prepared of such feeble resistance that once introduced into the tissues none multiply. In the preparation of vaccines killed by heat or other agents, the first question to present itself is the significance of the factor of virulence in the cultures used. Should the organism possess as nearly as possible its normal parasitic functions, or should it be attenuated? If the body in its attempt to rid itself of parasitic invaders must meet all aggressive and defensive forces of the parasite, we should say unqualifiedly that the vaccine should consist only of highly invasive organisms, suitably killed. If, on the other hand, there are only certain activities, certain products of the microbe that must be attacked by the host to promote resistance, all others in the vaccine would be a hindrance.

It has been stated from time to time that highly virulent strains of cholera, bubonic plague, and typhoid, used as vaccine after they have been killed by heat or chloroform, are too toxic for use. It may be questioned in answer to these objections to virulent strains whether too large doses were not used and whether minute doses of virulent strains would not accomplish what large doses of nonvirulent strains are expected to do. In future more precise studies of specific vaccines, the quantitative aspect will need attention. Hitherto gross, qualitative differences have been aimed at. In fact, in the use of killed bacteria practice has outrun experimental analysis, as has been so common in medicine.

It would seem relatively easy to demonstrate the action of vaccines on animals, but this is not true. Infectious diseases which have become definitely established among animals induce disease in only a certain variable percentage of the animals exposed, and the attack varies much chronologically. Here also large numbers of cases are indicated if the result is to take any definite shape. Hitherto little interest has been developed in this field, partly because animal diseases had not been studied, partly because it was difficult to anticipate whether inferences based on such studies would be accepted as holding true for related infectious processes in the human subject. Human medicine has been capricious in this respect, for it has swallowed avidly many conclusions and inferences based on analogy and entirely ignored or denied the validity of others of equal or better repute as scientific data. In general, it may be stated that bacteria killed by heat have not as yet proved successful in animal diseases. Pasteur tried them in anthrax and failed, as Duclaux tells us. Although they may give rise to a

relatively high concentration of agglutinins, the actual protection afforded is slight. This has been found true in experimental paratyphoid when the races vaccinated against have distinctly invasive characters. The method, however, deserves continued trial since diseases caused by certain groups of bacteria, such as the bipolar bacteria, are distinctly influenced by vaccines made from heated cultures.[1] The agglutinin titer, however, hardly represents more than that a certain number of bacteria bodies have passed through the host organism, and it should not be interpreted necessarily as increased resistance. The generally accepted effect of heated cultures of typhoid bacilli in protecting against typhoid is not doubted. It should, however, stimulate further inquiry into the nature of the disease to discover how such an effect is explainable. It is highly probable that the human race is already well protected against this highly saprophytic organism and a slight impulse may be sufficient to ward off invasion, not so much of the intestinal tract and multiplication there, as of subsequent entry and multiplication in the lymphatic tissues.

The use of heated cultures has now been advanced into the therapeutic field. There is no good reason to assume that the principles governing prophylactic and therapeutic application are essentially different. For the rational application of such vaccines an exact knowledge of the processes of infection and recovery is far more urgent than in preventive vaccination, for there is danger of doing injury. The important problem is the elimination, if possible, from the vaccine of all factors not immediately concerned in the curative reaction. In the nature of things such elimination may remain a pious hope, but it is essential that the effort be made.

Another most important development of clinical medicine to all appearances not in harmony with current theories of resistance and how it is acquired, is the tendency to eliminate all superficial, local foci of infection as dangerous to the individual. Local foci probably, from time to time, give off agents into the circulation. These, however, are presumably kept in check by the influence of the local process. When such a focus is removed and agents still disseminated in the body, are they more or less dangerous than before? Obviously a number of conditions enter into this problem, which need more experimental study before either clinical medicine or immunology may speak the last word.

There remains to be considered the effect of general immunization on the race as a whole. In the unrestricted interplay of natural forces

among animals, disease has little chance of gaining a foothold because the animal must possess a certain degree of strength, instinct, and native skill to survive. This is true of solitary as well as gregarious animals. In the human race, the formation of groups and the capacity of the group to protect itself within limits from natural enemies leads to the survival of large numbers of what might be called inferior varieties and the permanent domiciling of various types of disease in such populations. Through the intermingling of types of widely different geographic and climatic origins various degrees of susceptibility to parasitism prevail. There are those at one end that are fatally susceptible, at the other markedly resistant. In between are degrees of resistance and susceptibility. These varieties, if plotted, would probably give us a normal frequency curve of the usual type. The relative susceptibilities on the part of the host species and the activity of the virus or the parasites maintain themselves subject to fluctuations in the environment, through the continual appearance of spontaneous variations on the part of the hosts and the continual adjustment to these on the part of the parasite.

To this self-regulating reaction between host and parasite which tends automatically to eliminate all those individuals near one end of the negative side of the mean, we apply a protective vaccine. What will be the result? The answer to this question cannot be given on the basis of any experience possessed by the human race concerning itself or its domesticated animals. Although vaccination against smallpox has been quite generally practiced for half a century, the measures for preventing the dissemination of the virus through isolation and quarantine have been more rigorously applied than vaccination itself. Moreover, it is a disease quite readily recognized in its early stages and there are presumably no healthy carriers. Evidently largely conceived and thoroughly executed experiments on different types of infectious animal diseases must provide fundamental data for the solution of our question.

Concerning the results of immunization with dead typhoid bacilli, the time is still too short to yield any general inferences of definite value. The general application of a successful vaccine in this disease should at first lead to a distinct lowering of morbidity and mortality. If the same methods of disinfection of discharges obtain as are now current, and if the great communal streams of milk and water are supervised to prevent undue pollution, we should expect, after several

generations, the appearance of variants having less as well as more resistance. This would be registered by a wave of higher morbidity and mortality in spite of the vaccination. Such waves might be expected periodically even with generally applied vaccination. By such reasoning we may account for the difficulty of depressing diphtheria mortality below a certain level and the occasional appearance of epidemic waves. The gist of the matter is that though the plane of resistance is raised, the same phenomena will go on on this higher plane as were witnessed before vaccination. The one practical argument which emerges from such analysis is that any efficient vaccination once in operation must be generally applied, and it cannot be discontinued without a simultaneous higher morbidity and mortality for one or more generations. The important problems caused by the general use of a vaccine, such as the appearance of modified types of disease, the relative increase or decrease of so-called carriers and the possible appearance of modified races of bacilli, can only be solved by cooperation on a large scale.

Perhaps the greatest benefit which vaccination might confer on the human race would be a lightening of the enormous and increasing burden of trying to intercept too thoroughly the streams of infection. The generation just passed has witnessed the application, on a huge scale, of methods intended to stop these streams. They have been applied by continent against continent, state against state, community against community, and individual against individual. They are responsible for a great costly public health machinery and for numerous daily restrictions in the life of the individual. The need for restricting and suppressing wherever possible the currents of infection will continue in order that the increasing danger of a growing population may be met. It is safe to say that the machinery set up for this purpose by public health agencies cannot check completely any stream of infection. Its success is quantitative rather than qualitative. It keeps the dose of infection down and reduces its frequency. We may take courage from the fact that in a population in which a given disease has prevailed for some time, a small dose of certain viruses may produce little disturbance while it immunizes toward a future possibly larger dose. There is, therefore, going on constantly some protective inoculation of which we are usually quite unaware. This factor, the destruction of virus in the patient's environment, and what vaccination is practiced constitute the triumvirate which is endeavoring to keep parasitism within safe limits. It cannot be wholly eliminated for it involves a

universal activity of life itself. A most important final problem bearing on the best interests of the race itself is for us to learn how far to go in the destruction of parasitism and how much to sacrifice to this end.

In presenting to you from a comparative, biologic standpoint methods of protective inoculation, whether or not such methods could be used today on the human being, I have had two reasons. In the first place, the illustrious scientist in whose name you have established a foundation lecture to stimulate research had no conventions as to the nature of the material on which to test his scientific intuitions. His medical work, on which much of his fame rests, was done on diseases of animals and essentially those species which were useful to his fellow men. Throughout his career he attacked practical problems.

The second reason for dealing with immunization from a more general standpoint than that afforded by practices in human medicine is the possibility that in the future either through urgency or because of better methods, living vaccines may be used on human beings to mitigate the blow of diseases that tend to break through all barriers put in their way. Medicine should be prepared, through as thorough an understanding of disease processes as the progress of science affords, to evaluate the virtues and defects of all methods aiming at the same final result and thus be ready to apply them when the need presents itself.

FAULTY FOOD IN RELATION TO GASTRO-INTESTINAL DISORDER

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I propose in this lecture to propound the thesis that much of the gastro-intestinal disorder of civilized peoples at the present day is due to faulty food. In doing so I shall present evidence of the incidence of such disorder among civilized communities and of its comparative absence among certain races living under more natural conditions; and contrast, in general terms, the food habits of the former with those of the latter. I shall refer to the special relation of perfect food to the functional perfection of the gastro-intestinal tract; and from these sources advance presumptive evidence of the effects of faulty food in impairing the functional perfection of the digestive system. Experimental evidence of these effects will then be given, and attention directed to the applicability of the experimental results to the genesis of certain acute and chronic gastro-intestinal disorders. Finally, I shall argue that faulty foods capable of causing similar effects in man to those produced experimentally in animals are widely made use of at the present day. Having thus introduced the subject to your notice I shall leave you to examine for yourselves in the wards, the clinic and the home the truth of the doctrine I have propounded.

PREVALENCE OF GASTRO-INTESTINAL DISORDERS AMONG CIVILIZED PEOPLES

It was recently stated by a public health administrator in England that 25 per cent. of all patients seeking relief at our clinics did so for gastro-intestinal disorders. So far as my memory serves me, the statement was made in order to emphasize the necessity for a study of the etiologic factors concerned in the production of this great mass of sickness. It has, too, been pointed out within the last few months that the alarming increase of cancer among town-dwellers in Great Britain is due, in the main, to the increasing prevalence of gastro-intestinal cancer. These are facts of such public concern that they demand the close

attention of all students of public health; for if by any means we can prevent gastro-intestinal disorders we shall relieve civilized communities of one quarter of their sufferings.

In the fascinating pursuit of pathogenic organisms as causes of disease, we are apt to overlook the claims on our consideration of sufferers from noninfectious maladies—the claims, for instance, of the dyspeptic or of the sufferer from colonic disease. Possiby this is due to the fact that the dyspeptic rarely dies of dyspepsia nor the subject of colonic disease from colitis. Their discomforts, not being catching, are no more to their neighbors than a source of irritation; consequently their claims on the consideration of the hygienist are overshadowed by the multitude's demand for the elimination of the microbe. The multitude does not know, and we ourselves often forget, that the activities of the microbe as a pathogenic agent are very often dependent on those very conditions of life which give rise to the discomforts and sufferings of the victims of such maladies as indigestion and mucomembranous colitis. It is these conditions of life and of imperfect nutrition which frequently prepare the soil of the body for the rank growth of bacterial agents.

Fortunately, within the last few years the attention of investigators of disease has been directed into new channels of inquiry, channels which take cognizance of the influence of negative factors in the production of disease as well as of positive factors. As is usual in any new development, advance has been made along narrow lines; but the stream of knowledge has gradually broadened, so that we are beginning to appreciate the wider significance of the negative factors in the production of disease in general. Chief among them is food deficient in some ingredient essential to the body's well-being, such, for instance, as vitamins, suitable protein, iodin, phosphorus or calcium. It sometimes happens that one such essential is present in the food in insufficient quantity. Then metabolic harmony ceases or becomes discordant and "deficiency disease" results.

It is necessary to emphasize that "deficiency disease" is a question not merely of deficiency of vitamins, but of deficiency of any essential requisite of a perfect food. Nor is this all, for in practice deficiency of one essential often means excess of another; such, for instance, as relative deficiency of vitamin B in the presence of an excess of starch, or relative deficiency of iodin in the presence of an excess of fats; the excesses may themselves give rise to relative deficiencies of other

essentials, and especially of those present in the food in relatively small quantities. Lack of balance of the food is a fault second only in importance to actual want of some essential ingredient. The food faults encountered in practice are thus often compounded of deficiencies in association with excesses.

The importance of adequate food-balance is illustrated by even the purest of "deficiency diseases," such as scurvy, concerning which Pitz and Lewis have shown that adequate provision of other food essentials will delay in guinea-pigs the onset of scurvy, induced by lack of vitamin C, and prolong their life. The same is true of other deficiency diseases, such as polyneuritis columbarum induced by lack of vitamin B. My own researches have impressed the importance of perfect food balance on me with increasing force within the last few months, since I have been able to show that an excess of fats or of unsaturated oleic acid in the food may cause a relative deficiency of iodin and enlargement of the thyroid gland (goiter). It is necessary also, in this connection, to recognize a further fact, namely, that one cannot in practice dissociate from the effects of deficient and ill-balanced foods those of bacterial or protozoal agencies whose ravages have been made possible by the faulty food. My remarks today, therefore, are to be considered from these broader aspects, namely, of food deficiencies in association with food excesses, and with the fortuitous intervention of microbic or other pathogenic organisms.

FREEDOM OF UNCIVILIZED RACES FROM GASTRO-INTESTINAL DISTURBANCES

In considering gastro-intestinal disease in the mass, the realization is forced on one that since it is so common it must have a very common cause. It is helpful, in endeavoring to ascertain the cause of a malady widely prevalent in one community or race, to contrast the conditions of life of such a community with those of another that is free, or comparatively free, from the malady in question. My own experiences have afforded me this opportunity in the case of gastro-intestinal disorders. For some nine years of my professional life my duties lay in a remote part of the Himalayas where there are located several isolated races far removed from the refinements of civilization. Certain of these races are of magnificent physique, preserving until late in life the characters of youth; they are usually fertile and long lived, and endowed with nervous systems of notable stability. Their longevity

and fertility were, in the case of one of them, matters of such concern to the ruling chief that he took me to task for what he considered to be my ridiculous eagerness to prolong the lives of the ancients of his people, among whom were many of my patients. The operation for senile cataract appeared to him a waste of my economic opportunities, and he tentatively suggested instead the introduction of some form of lethal chamber designed to remove from his realms those who by reason of their age and infirmity were no longer of use to the community. Among another of these races, the custom which required an eldest son on pain of death to carry in a conical basket his aged and decrepit parents to the top of a high rock from which to hurl them to destruction has died out only within recent years under the protective influence of British rule; and the proverb "Everyman's basket for his son" still survives the custom.

During the period of my association with these peoples I never saw a case of asthenic dyspepsia, of gastric or duodenal ulcer, of appendicitis, of mucous colitis, or of cancer, although my operating list averaged 400 major operations a year. While I cannot aver that all these maladies were quite unknown, I have the strongest reason for the assertion that they were remarkably infrequent. The occasions on which my attention was directed to the abdominal viscera of these people were of the rarest. I can, as I write, recall most of them; occasions when my assistance was called for in the relief of strangulated hernias, or to expel the ubiquitous parasite Ascaris lumbricoides. Among these people the "abdomen oversensitive" to nerve impressions, to fatigue, anxiety or cold was unknown. Their consciousness of the existence of this part of their anatomy was, as a rule, related solely to the sensation of hunger. Indeed, their buoyant abdominal health has, since my return to the West, provided a remarkable contrast with the dyspeptic and colonic lamentations of our highly civilized communities. Searching for an explanation of this difference in incidence of gastro-intestinal disease in the two peoples, I find it, in the main, in four circumstances: (1) Infants are reared as Nature intended them to be reared—at the breast. If this source of nourishment fails, they die; and at least they are spared the future gastro-intestinal miseries which so often have their origin in the first bottle. (2) The people live on the unsophisticated foods of Nature: milk, eggs, grains, fruit and vegetables. I don't suppose that one in every thousand of them has ever seen a tinned salmon, a chocolate or a patent infant food, nor that as much sugar

is imported into their country in a year as is used in a moderately sized hotel of this city in a single day. (3) Their religion prohibits alcohol, and although they do not always lead in this respect a strictly religious life, nevertheless they are eminently a teetotal race. (4) Their manner of life requires the vigorous exercise of their bodies.

FAULTY FOOD

Each one of these differences in the habits of my Himalayan friends, as compared with those of Western peoples, would form, in itself, a fitting subject for discourse; but I shall content myself with a brief consideration of the first two under the general heading of "faulty food." It is not that the races to which I have referred live under hygienic conditions superior, as to housing and conservancy, to those of the masses in the West. On the contrary, in both these respects their conditions of life are most primitive. Nor is it that in their agricultural struggles with Nature they have acquired any peculiar immunity to the effects of faulty food; they are, indeed, as susceptible as others to these effects, as the following occurrence illustrates: It fell out that the cultivable lands of one of these races were no longer sufficiently extensive for the increasing population. To meet this it was decided to colonize another tract which had never previously been cultivated. A dozen families were settled there, and they made shift to grow upon its granite and infertile soil such grains as they could. My attention was directed to their efforts, and more especially to the results of them, when ten out of twelve adult young men developed paralysis of the lower limbs due to lathyrism—a rare malady resulting from the disproportionate use in the food of the vetch Lathyrus sativus. These settlers, finding it impossible to grow a sufficiency of wheat, had cultivated the hardy vetch and used it in too high admixture with their scanty stores of wheat. The result was the development of paralysis of the lower limbs among the male population, while the female members of the settlement were unaffected. I mention this dramatic occurrence to show you that perfect physique and stability of the nervous system did not protect them from the effects of faulty food, and incidentally to emphasize the sex variations to be found in maladies resulting from food faults. For although in the case of lathyrism the difference in incidence of the disease in the two sexes is more marked than in any other nutritional malady known to me, yet it is in some nutritional diseases a very striking feature.

We see, then, that as exemplified by certain Himalayan races and, as I find from recent reports in the medical press, by such races as those of upper Egypt and northern Nigeria, enforced restriction to the unsophisticated foodstuffs of Nature is compatible with fertility, long life, continued vigor, perfect physique and a remarkable freedom from digestive and gastro-intestinal disorders, and from cancer. I must confess that with these examples before me I find myself in accord with Hindhede, who affirms—and on unequivocal evidence—that the two chief causes of disease and death are food and drink.

CONTRAST BETWEEN FOOD HABITS OF PRIMITIVE PEOPLES AND THOSE OF CIVILIZED COMMUNITIES

Let us now for a moment contrast the habits of these primitive peoples in respect to food with those of our more highly civilized communities. The former are content with natural foods: milk, eggs, grains, fruits and leafy vegetables—or, if their state of mind be not precisely one of contentment, they can at least not better their lot nor worsen it. These natural foods—"the protective foods," as McCollum has named them—provide in proper quality and proportion the proximate principles and vitamins necessary for nutritional harmony, and the proper vegetable residues for the healthy evacuation of the bowels. But the case is different with civilized man. No longer is he content with the unsophisticated foods made in Nature's laboratory, with "herbs bearing seed" and with "every tree in which is the fruit of a tree yielding seed." To him these are "still for meat," but preserved, purified, polished, pickled and canned. Some he extracts and distils with the object of procuring concentrates agreeable to his taste. His animal food he heats, dries, freezes, thaws and stores. One way or another by desiccation, by chemicals, by heating, by freezing and thawing, by oxidation and decomposition, by milling and polishing, he applies the principles of his civilization—the elimination of the natural and the substitution of the artificial—to the food he eats and the fluids he drinks. With such skill does he do so that he often converts his food into a "dead" fuel mass, devoid of those vitamins which are to it as the magneto's spark to the fuel mixture of a petrol-driven engine. Unmindful, too, or more often ignorant, of the composition of the fuel-mixture with which he charges his human machine, he joins deficiencies of some essentials with excesses of others, heedless that the smooth running of his bodily functions bears intimate relation to the ordered balance of these essentials.

I am not at the moment concerned with the circumstances of his civilization—expediency, penury, prejudice, ignorance or habit—which have compelled man into this dangerous course. It is sufficient for my purpose that these circumstances exist, and that, in consequence of the food habits they have fostered, normal bodily function cannot be sustained and gastro-intestinal function is one of the first to suffer. Let me emphasize this point: "Gastro-intestinal function is one of the first to suffer." This truth is made manifest by the clinical evidences of disease that are first to appear in wild monkeys fed on deficient and ill-balanced food: loss of appetite, depraved appetite, vomiting, diarrhea, dysentery, anemia, unhealthy skin, asthenia, and loss of body-weight. If the faulty food be persisted in, other symptoms manifest themselves later, due in the main to malnutrition of the central nervous system; but it is the gastro-intestinal tract, the functions of digestion, absorption and assimilation that are among the first to fail in consequence of faulty food. These are the signs that our ship is running upon the rocks and, as good pilots, we must be aware of them. I often think that we are apt to assume more readily the office of salvors of wrecks than of pilots whose function it is to prevent them.

But not only is functional failure of the digestive system an early evidence of faulty food, but the gastro-intestinal tract is often the first to exhibit clinical evidence of infection by pathogenic organisms in consequence of it. Let me illustrate this last point by an experience in my own laboratory: Thirty-six wild monkeys were captured in the jungles of Madras and transported with the least possible delay to my laboratory in the hills at Coonor. They were in perfect health and full of vigor—wild things usually are. I had in these animals perfectly normal tissues to work on: a unique opportunity to observe the first clinical and pathologic effects on normal tissues of the agent —faulty food—with which I was working. Each of these animals was placed in a separate cage, and all were confined in the same animal room. One attendant looked after them all. Twelve of them were fed on natural food, the remaining twenty-four on food deficient in some cases in vitamins as well as ill balanced; others were fed on natural food in which the living essences had been destroyed by sterilization. Those that were naturally fed remained free from intestinal disease; those that were fed on deficient and ill-balanced food and on sterilized food developed, within a short time in the majority of cases, diarrhea or actual dysentery. Here, then, is an unequivocal instance not only

of the effect of faulty food in inducing a specific disease such as dysentery but of the protection against it that is afforded by a natural and well-balanced food.

RELATION OF PERFECT FOOD TO FUNCTIONAL PERFECTION OF GASTRO-INTESTINAL TRACT

Now let us consider for a moment the purposes which perfect food subserves. Every one recognizes that food is taken into the body to repair tissue waste, to supply energy, and to provide the proper medium for the chemical reactions of the body. But do we always visualize these functions of food in relation to the organs of digestion themselves, and to the work to be done by the gastro-intestinal tract? If we did, I think we should have no difficulty in realizing the special effects on these organs of an insufficient supply of proteins which rebuild the digestive tissues and make good their waste, or of those constituents of the food which supply energy for the production of the digestive secretions and the movements of food along the digestive tract, or of salts which provide the proper medium for the chemical processes of digestion, or of vitamins which activate the cells of the digestive system to healthy function. The effects of deficiency of these essentials must of necessity be manifested in failures of digestive, absorptive, assimilative and motor functions of this important region of the body. It is not necessary to make laboratory experiments to prove that if a woman lives on white bread, margarin, condensed milk and tea with a minimum of imported meat and boiled potatoes she is prone to suffer from such digestive disorders as dyspepsia and colonic disease. For such a diet does not contain a sufficiency of proteins to rebuild the tissues involved in digestion, assimilation and evacuation of the bowel contents; it does not contain a sufficiency of vitamin to activate the cells of the digestive system to healthy function; it is ill balanced, and by its excessive richness in starch it favors the development in the digestive tract of fermentative organisms, and makes relatively more deficient the vitamins necessary to healthy cellular action; nor does it contain a sufficiency of vegetable residue, of cellulose, waxes and vegetable salts, to insure natural action of the bowels.

EFFECTS OF FAULTY FOOD

Nor do we, I think, always consider the dependence of one constituent of the food upon another for its share in the maintenance

of nutritional harmony. We know that if such essentials as protein and inorganic salts be not provided in adequate quality and quantity, growth must flag and repair of body waste must fail or cease; but do we realize that the utilization of suitable protein and of suitable salts is dependent on the presence in the food of a sufficiency of vitamins, or that the efficiency of vitamins is dependent in considerable measure on the adequate supply of these proximate principles? If the tissue waste of the gastro-intestinal tract be not made good—whether in consequence of insufficient supply of suitable protein or of its insufficient utilization—then must the production of digestive juices fail, the mechanism of absorption and assimilation flag, the neuromuscular control of the gastro-intestinal tract become inefficient and the tissues of the tract become the prey of pathogenic organisms. It is thus that such a nutritional disease as pellagra arises, and thus that the manifold varieties of gastro-intestinal disorder due to failure of digestive function may come into being.

It is unwise to consider any of the essential ingredients of food, whether proteins, carbohydrates, fats, salts, water or vitamins, as independent of the assistance derivable from their associates in the maintenance of digestive and nutritional harmony. No doubt, some of these have special relations to others, as for instance that of iodin to fats, that of vitamin B to carbohydrates, that of vitamin A to lipoids, calcium and phosphorus holding substances, and that of vitamin C to inorganic salts. But whatever be their special relations one to another they are all links in the chain of essential substances requisite for the harmonious regulation of life's processes: if one link be broken, the harmony ceases or becomes discord. Of late the science of nutrition has tended to assume a too "vitaminic" outlook, and it is well to realize that, important as these substances are, man cannot live on vitamins alone, nor can he live on proximate principles alone: each is complemental to the other, and deprivation of the one leads to starvation as surely as does deprivation of the other. Our knowledge of vitamins is still in the making, but it serves a useful purpose to have some mental conception of their function. I have likened it to the magneto's spark which ignites the fuel-mixture of a petrol-driven engine, liberating its energy: the spark is of no use without the fuel nor the fuel without the spark; nay, more, the efficacy of the spark is dependent in great measure on the composition of the fuel-mixture.

EVIDENCE OF THESE EFFECTS

But if I am to succeed in demonstrating the truth of my claim that faulty food is responsible for much of the gastro-intestinal ill health so common at the present day, I must provide other than presumptive evidence of its effects on the digestive system and convince you also that foods having faults capable of causing these effects are nowadays extensively used by civilized communities. I propose, therefore, to fulfil the first condition by ocular demonstration and to rely upon my argument for the fulfilment of the second.

For some years past I have been engaged in a study of the effects of deficient and ill-balanced food on the various organs and tissues of the body, as observable in animals fed on such foods under experimental conditions. Having reached certain conclusions with respect to the digestive organs and gastro-intestinal tract in such animals as pigeons, rats and guinea-pigs, I repeated my experiments in wild monkeys captured in the jungles of Madras so that I might observe the effects of faulty foods on animals closely related to man. The foods I used were natural foods that had been rendered faulty by various means; they were of several classes:

1. Foods deficient in all three classes of vitamins, in suitable protein, in fats and excessively rich in starch.

2. Foods deficient in vitamins B and C and excessively rich in starch and fats.

3. Foods deficient in vitamin C only, in vitamin B only, and in vitamins A and B, but well balanced in other respects.

These classes of food presented for my purpose an adequate range of deficiencies alone, and of deficiencies in combination with excesses; they include many of the food faults observable in the dietary of many civilized people at the present day. Before demonstrating the effects of these faulty foods on the digestive organs and gastro-intestinal tract, I must point out very shortly the simultaneous effects to which they give rise on the endocrine regulators of metabolism, the thyroid gland, the suprarenal gland, and the pituitary body; for it is to be remembered that the maintenance of healthy gastro-intestinal function is dependent in considerable measure on healthy endocrine action. It would carry me too far afield to develop adequately the latter theme: I content myself, therefore, with directing your attention to it, and with laying emphasis on the fact that it is necessary to con-

sider in relation to the changes produced in the digestive system by faulty food those that are simultaneously produced by the same agency in the endocrine system. As an instance of this intimate correlation of digestive and endocrine function and disorder, I may refer to the simultaneous production by faulty food of colitis, of depreciation of liver function, and of suprarenal derangement. The first is the most obvious clinical feature of the nutritional disturbance induced by the faulty food; the occurrence of the second may serve to account for the toxic symptoms from which the sufferers from mucous colitis suffer, and for the opinion held by some that mucous colitis is due to hepatic insufficiency; while the third provides some insight into the effects of fatigue, anxiety and cold in precipitating attacks of mucous colitis in the malnourished subjects of colonic disease. The malady is, indeed, as much a disorder of the suprarenal glands as of the colon.

The data afforded by specimens indicate that the profound changes resulting in the gastro-intestinal tract in consequence of the various deficient foods employed are similar in kind in the three species of animals I used—pigeons, guinea-pigs and monkeys; it may be expected, therefore, that they will be similar in kind, if not in degree, in human beings whose dietaries have faults similar in kind if not in degree to those used in the experiments. I think there is good reason to believe that the prolonged use of a moderately faulty food will lead to them as certainly as the less prolonged use of a more faulty food. Without attempting to analyze them too closely or to attribute to each fault a specific effect we may, I think, draw from them certain broad conclusions:

1. The health of the gastro-intestinal tract is dependent on an adequate provision of vitamins. The absence of growth vitamins is capable of producing pathologic changes in the tract which frequently assume the clinical form of colitis. This observation is of the highest importance in view of the frequency with which this malady is encountered at the present day. Deficiency of vitamin C is especially concerned in the production of congestive and hemorrhagic lesions in the tract, and evidences of these may be found in animals which have not exhibited during life any of the clinical manifestations of scurvy in noteworthy degree. A state of ill health of the gastro-intestinal tract may thus be a prescorbutic manifestation of disease due to insufficiency of this vitamin, especially when associated with an excess of starch or fat or both in the food.

2. The disorder of the gastro-intestinal tract consequent on vitamin deficiency is enhanced when the food is ill balanced.

3. The pathologic processes resulting in this situation from deficient and ill-balanced foods are:

(a) Congestive, necrotic and inflammatory changes in the mucous membrane, sometimes involving the entire tract, sometimes limited areas of it.

(b) Degenerative changes in the neuromuscular mechanism of the tract, tending to dilatation of the stomach, ballooning of areas of small and large bowel, and probably also to intussusception.

(c) Degenerative changes in the secretory elements of the tract—of the gastric glands, the pyloric glands, the glands of Brunner, the glands of Lieberkühn, and the mucous glands of the colon. These changes are such as must cause grave derangement of digestive and assimilative processes.

(d) Toxic absorption from the diseased bowel, as evidenced by changes in the mesenteric glands.

(e) Impairment of the protective resources of the gastro-intestinal mucosa against infecting agents, due to hemorrhagic infiltration, to atrophy of the lymphoid cells, and to imperfect production of gastro-intestinal juices. This impairment not only results in infections of the mucous membrane itself, but also permits of the passage into the blood stream of micro-organisms from the bowel.

(f) It is to be emphasized that the pathologic changes found in the gastro-intestinal tract are more marked in some individuals than in others; and that, while all of them may occur in one and the same subject, it is usual to find considerable variation in the incidence of particular lesions in different individuals.

Applicability of Experimental Results to Genesis of Gastro-Intestinal Disorders

With these evidences of the effects of faulty food before us, we have, I think, good reason to proceed with our investigation of the relation of faulty food to the common gastro-intestinal disorders of the present day.

It is usually accepted as a proof of the causation of a malady that if an investigator by one agency or another can produce in animals, under controlled experimental condition, the malady in question, then this agency is the cause of the disease, or intimately associated with its

causation. Consider, then, that by means of faulty food, (1) diarrhea, (2) dysentery, (3) dyspepsia and gastric dilatation, (4) gastric and duodenal ulcer, (5) intussusception, (6) colitis and (7) failure of the colonic function can be produced experimentally. I do not argue that they are invariably so produced or that faulty food is the only cause of them. I do not deny the influence of microbic or other pathogenic agents in contributing to their production; indeed, I have ever insisted upon it. But I do maintain that faulty food is often at the bottom of their causation, and that the use of natural or well-balanced food from birth onward will greatly militate against their occurrence.

I cannot remember that by means other than faulty food such a disorder as colitis can be so readily produced, if at all; for the experimental production of amebic dysentery by the oral administration of Endameba histolytica cysts is not at all convincing. On the other hand, I have seen amebic dysentery arise in deficiently fed wild monkeys, while others that were well fed escaped the disease although subjected to the same risks of infection. In this instance, malnutrition had enabled the specific organism to implant itself in the tissues of the bowel. If further evidence of the influence of faulty food in the production of these gastro-intestinal disorders be needed, it will be found in abundance in the medical history of the late war, during which these disorders were so often the consequence of faulty food. In this regard, our enemies have served unwittingly one useful purpose: they forced us to concentrate attention on the immediate and remote effects of food faults on the human body. But our ever present enemies in peace—poverty, prejudice, ignorance, habit—are no less responsible in this regard; they, too, beneath the vaunted culture of our civilization, inflict upon numbers of our people an intolerable load of misery, which it is our duty to relieve.

I would, therefore, urge on your attention a consideration of the effects of faulty food in relation to such acute disorders as infantile diarrhea, jail dysentery and asylum dysentery, asking you, while remembering the bacteriologic aspects of these maladies, to look on them also from the point of view of faulty food. The bacteriologic path has led us far in our knowledge of preventable disease, but it will lead us further still if we traverse at the same time the paths of malnutrition that so often run parallel with it. In relation to such chronic disorders as "mucous disease" in children, chronic gastro-

intestinal dyspepsia, pellagra sine pellagra, colonic disease in adults, celiac disease, gastric and duodenal ulcer, and chronic intestinal stasis, the food factor in their production deserves the fullest consideration; for if the facts I have laid before you do not provide the whole explanation of their genesis, they are, I am convinced, intimately related to it. Time does not permit me to develop this theme further. Full reference has been made to it in my recently published book, "Studies in Deficiency Disease," where many points which of necessity I have omitted from this lecture are set out.

EXTENSIVE USE OF FAULTY FOOD

Turning now to my last duty, that of presenting evidence that faulty food is largely used by many civilized people at the present day, I would ask you to consider first in this connection the increasing tendency in modern times to rear infants artificially—on boiled, pasteurized and dried milks, and on proprietary foods which are all of them vastly inferior to the healthy mother's milk in substances essential to the well-being of the child—inferior not only in vitamins, but also in enzymes, thyroid derivatives and other essentials. When, as is sometimes the case, mother's milk is itself harmful to the child, is not this largely the result of her own disordered metabolism that in many cases results from improper feeding before, during and after pregnancy? For mother's milk may, like the milk of animals, be deficient in certain respects if her food be deficient. The milk of stall fed cows is not so rich either in vitamin A or in vitamin C as that of cows fed in green pastures.

Again, is not cow's milk—an important dietary constituent of young and old alike—gradually becoming a luxury reserved for the few? Vegetable margarins are replacing butter even among the richer classes. Fresh fruit, certainly in Great Britain, is a comparative rarity, even on the tables of the rich. Green vegetables are scanty, and such as there are are often cooked to the point of almost complete extraction of their vitamins and salts. White bread has largely replaced whole-meal bread, and it is notorious that bread forms a high proportion of the dietaries of persons of limited means. It is notable that, despite the food restrictions imposed upon the people of Belgium during the late war, the infant mortality and infantile diarrhea decreased greatly—a circumstance which was due to the organized propaganda encouraging mothers to nurse their infants, and to the establishment of national

canteens which provided prospective mothers from the fifth month of pregnancy onward with eggs, meat, milk and vegetables. Again, fresh eggs are so expensive as to debar the masses from their use. Meat is at best but poor in vitamins, and its value in these essentials is not enhanced by freezing and thawing. Sugar is consumed in quantities unheard of a century ago, and sugar is devoid of vitamins which the cane juice originally contained. The use of stale foods involving the introduction of factors incidental to oxidation and putrefaction is the rule; that of fresh foods, the exception.

Can it, then, truly be said that the variety of natural foodstuffs consumed by Europeans protects them from any deficiency of vitamins? My own clinical experience justifies no such belief; rather does it point in the contrary direction. Nor does it appear to be the experience of the compilers of the Thirty-Eighth Report of the British Medical Research Council, who write: "From a consideration of dietaries consumed by the poorer classes in the towns of Great Britain, one is led to suggest that no inconsiderable proportion of the population is existing on a food-supply more or less deficient in fat-soluble factor"—deficient, that is to say, in a vitamin one of whose cardinal functions is to maintain the natural resistance of the subject against infections. That similar considerations apply in this country also appears from the experience of Osborne, who asserts that a large part of the food eaten by civilized people has been deprived of Vitamin B by "improvements" in manufacture, and of Hess, who emphasized that latent and subacute forms of scurvy due to insufficient intake of vitamin C are common disorders of infancy.

But the frequency with which deficient and ill-balanced foods are used is most apparent when the dietetic habits of persons in subnormal health are considered. It will surprise those who study them to find how many there are, of capricious appetite, who habitually make use of foods sometimes deficient in calories—for it is not the food presented to the subject that counts, but the food eaten and assimilated—and often dangerously deficient in one or more vitamins, in protein of good biologic value, and disproportionately rich in starch or sugar or fats, or in all three. Infants fed on many of the proprietary foods in common use come within the category of the deficiently fed, unless deficiencies are made good. The food of young children is commonly low in vitamin content, and in suitable salts and protein, while it is frequently disportionately rich in starch and sugar—a circumstance which enhances

the danger of vitamin deficiency. It may, indeed, be accepted as an axiom that the vitamin value of a child's food is reduced in proportion to its excessive richness in carbohydrates.

But the ranks of the deficiently fed include not only infants and young children; they include also those whose food is composed mainly of white bread, margarin, tea, sugar and jam, with a minimum of meat, milk, eggs and fresh vegetables. Even among those whose diet is more perfectly balanced, the commoner articles of food, as they are prepared for the table, are so low in vitamin value that, unless they are enriched with a sufficiency of natural foods in the raw state, they are prone to cause ill health, and especially gastro-intestinal ill health. Such is my experience in India, where this European patient "cannot digest vegetables or fruit," and never touches them, as they carry infection," or that one "suffers so from indigestion" that he or she lives chiefly on custards and milk puddings; where milk is, of necessity, boiled and reboiled until, as a carrier of vitamins, it is almost useless; where meat is made tender by simple device of boiling it first and roasting it afterward; where every third or fourth European child has mucous disease, the direct outcome of bad feeding. So it is that the forms of food which such as these so commonly adopt are those most calculated to promote the very disorder from which they seek relief.

Access to abundance of food does not necessarily protect from the effects of food deficiency, since a number of factors—prejudice, penury, ignorance, habit—often prevent the proper use and choice of health-giving foods. Who in the ranks of practicing physicians is not familiar, among the well-to-do classes, with the spoiled child of pale, pasty complexion and unhealthy appetite, of sluggish bowel, and often with mucous stools or enuresis, who, derived of the wholesome ingredients of a well-balanced natural food, craves for sweetmeats, chocolates, pastries and other dainties as devoid of natural health-giving properties as their excessive use is common? Constantly one encounters the anxious mother of the "highly strung," "nervous" child "of delicate digestion," whose ignorance of essential principles of feeding is only excelled by her desire to do what is best for her offspring; who, guided by the child's preferences, supplies the means to convert it into a static, constipated, unhealthy-skinned adolescent, equipped with digestive and endocrine systems wholly unfitted to sustain the continued exercise of healthy function. Or, again, who is not familiar with the overworked anemic girl, static and with visceroptosis, acne or seborrhea,

and oftentimes with vague psychoses, who ekes out a paltry wage for teaching, sewing or selling, satisfying the cravings of her tissues principally with white bread, margarin and tea? Or with the languid lady, devoid of healthful occupation, who, living in the midst of plenty, deprives herself, for some imaginary reason, of substances essential to her well-being? Or with the harassed mother of children, oppressed with the constant struggle to make ends meet, stinting herself that others may not want, exhausted by childbearing and suckling, worry, and too little of the right food? What wonder that such a woman is dyspeptic, and that "every bite" she eats "turns on her stomach." Some there are, living in luxury, whom ignorance or fancy debars from choosing their food aright; others for whom poverty combines with ignorance to place an impassable barrier in the way of discriminating choice. It is for us so to instruct ourselves that we may instruct such as these, and use our newer knowledge to the end that customs and prejudices may be broken and a more adequate dietary secured for those under our care. We may, in our desire to promote the health, vigor and fertility of our people, learn much from the practical farmer or stock-breeder whose experience has taught him that all these evidences of normal functional activity of the animal organism are dependent in the main on one great factor—perfect food supply.

CONCLUSION

I trust that I have said enough to serve as an introduction to the study of this important subject, than which there is none more worthy of the consideration of those whose life is spent, or to be spent, in guarding the national health. It seems to me that in regard to it we have three obvious duties; the first, to instruct the masses as to what to eat and why to eat it; the second, to apply the results of our science to the production of natural foods in abundance and to their widespread and cheap distribution, rather than to the erection of institutions for the treatment of maladies due to their want; the third, and most important, ardently to pursue our investigations and the acquirement of knowledge. In no department of human endeavor are the words from the agrapha of Christ more pertinent than in their application to the study of the relations of food to health and disease:

> Let not him who seeketh, cease from seeking until he hath found:
> And when he hath found he shall wonder.

MEDICAL PERIODICAL LITERATURE

PRESIDENT'S ADDRESS, DEC. 6, 1921.

GEORGE H. SIMMONS, M.D.
Editor, Journal of the American Medical Association

The presidential address for an organization such as the Institute of Medicine should be devoted to a discussion of a scientific subject in which at least a majority of its members are interested. When I cast about for such a subject I realized that, if I attempted to select one of such character, I might flounder and get beyond my depth. But, as former presidents selected subjects related to their particular lines of practice or work, I have done the same. An intimate acquaintance of nearly thirty years with medical journalism has perhaps given me an exaggerated idea of its importance; my subject, however, is closely related to the advancement of medical science, and this would be my apology, if an apology were necessary, for selecting such a dry and prosaic subject as Medical Periodical Literature.

MEDICAL JOURNALS

In its earlier years, the American Medical Association conducted its scientific work through committees. In 1848, Dr. Oliver Wendell Holmes, who that year was chairman of a committee on medical literature, read a report which concerned medical journals and medical books, rather than medical literature itself, in which he said:

> In the course of half a century from the establishment of the first of the medical journals, their number has been gradually rising, until at the present time, at least twenty are known to be in existence.

What *would* Dr. Holmes say today! It is difficult to trace the growth of medical journals from 1848 until the early seventies; from that time it can be done roughly from newspaper and medical directories. During the period from 1870 to 1900, at least 450, probably nearer 500, medical journals were started, many leading an ephemeral existence of but a few months or years. The peak was reached in 1903, when there were a little over 230.

Seeking an explanation of the twenty periodicals of 1848, Dr. Holmes said:

> Some principle in addition to the wants of the reading community must exist to account for such inordinate fecundity in this particular department. This is to be found in the homely fact that a medical journal is a convenient ally and advertising medium for public institutions and publishing establishments.

He says nothing, it will be noted, regarding the medical journal's position as a convenient ally and advertising medium for proprietary medicines. The reason is simple: The proprietary medicine business, as we know it, did not exist; it developed and flourished during the thirty-five year period ending in 1905; and it was during this period that the truth of the saying, "Whose bread I eat, his song I sing" had a practical demonstration in both the reading and the advertising pages of the vast majority of the journals.

The number of medical journals began to decrease in 1905, and today there are approximately 120, as against 230, sixteen years ago. Not only has there been a decrease in number, but an entirely different class of journals has appeared—purely scientific journals unhampered by, and free from, selfish commercialism. I refer to such publications as the *Journal of Medical Research*, the *American Journal of Anatomy*, the *Journal of Infectious Diseases*, the *Journal of Biological Chemistry*, the *Journal of Bacteriology*, the *American Journal of Physiology*—to mention a few. Prior to 1900, only one of this class of journals existed: the *Journal of Experimental Medicine*.

About this time, also, state medical associations began to substitute monthly journals for their annual transactions. Today there are thirty state journals, representing thirty-six state societies.

My subject, however, is not medical journals nor medical journalism. I make this brief retrospect simply as a background for the main theme.

MEDICAL ARTICLES

There is a distinct change in the type of papers appearing in medical journals today as compared with twenty years ago. The therapeutic article of the past, replete with favorite prescriptions, often proprietary in character, has given way to scientific contributions on therapeutic methods, on pharmacology, on pathology, on etiology, on methods of diagnosis, on prophylaxis. The difference between then and now in this regard can be appreciated only by those who were in practice eighteen or twenty years ago, or by those who take the trouble to compare the journals of that period with the publications of today.

While there has been a decrease in the number of medical journals, there has been no decrease in the number of medical articles. During the first eleven months of the present year—up to December 1—there were voluntarily submitted for publication in *The Journal of the American Medical Association* 1,335 manuscripts. To the 1,335 must be

added 285 section papers, making a total of 1,620 for the eleven months, or approximately 1,750 manuscripts during the year. This is about the average for the last four or five years. A fair percentage of these papers were excellent, both in matter and in manner of presentation; many were valueless as scientific contributions, and not creditable as literary compositions. Between these two extremes was a greater number deficient either in matter or in manner—and more often the deficiency was in the manner of presentation.

We estimate that three fifths of the manuscripts voluntarily offered to *The Journal* for publication are returned. Why? What are the principal reasons for their rejection? With such a large number of papers, one would naturally suggest "lack of space" as the principal reason. And this would be partially, but not entirely, correct. No matter how many may be on hand, a well-prepared paper on a timely and practical subject—one that will appeal to a fair proportion of readers, especially to general practitioners—is accepted. A paper that is informative, that presents new facts or practical information, if fairly well written, is not returned.

Naturally, there are various causes for rejecting manuscripts, aside from lack of space: One is a plethora of material on one question, with the peril of devoting too much space to a given subject. This is likely to happen when a new treatment is introduced, a new theory advanced, or during and immediately after epidemics. The introduction of arsphenamin was followed by an ever-increasing lot of papers on the subject, all optimistic; Wright's opsonins and opsonic index produced a flood of articles of varying character; focal infection, long since threshed out, is still a live subject, judging from papers received, few of which contain new facts or new scientific evidence; the tonsils and tonsillectomy, and especially intruments for doing tonsillectomies, have been sadly overdone. After the armistice came a deluge of papers based on war experience, and the stream is not entirely dried up.

But, no matter how much a subject may have been discussed, or how much space may have been devoted to it, it is not overdone so long as new, worth-while facts, or new, scientific evidence, are forthcoming.

FANCIES VS. FACTS

Naturally, too, there are offered productions of theorists who, without scientific knowledge, have solved problems that are puzzling research workers and scientists. The number of physicians who have

the courage to discuss scientific problems, concerning the fundamental and elementary principles of which they are entirely ignorant, is larger than many imagine. Such papers usually are returned with the suggestion, circumspectly phrased, that an ounce of fact is worth a ton of theory.

That every physician has a right to express his opinions, to advance theories, and to make known his discoveries, is an accepted principle, and he should not be denied these rights by an editor without a good reason. But the reader has his rights also, and they should be paramount. He has the right to demand that the editor shall not publish fiction for fact or fallacies which he—the reader—is not qualified to detect. The editor is supposed to have knowledge of the author and of his dependability that the reader cannot have. The reader certainly may expect that the editor will comb out such material as is obviously false.

A few years ago a well-known physician sent for publication a paper in which he claimed that he had discovered a bacterial causative agent for a not uncommon, apparently noninfectious disease The discovery, if true, was epoch making. The average reader, especially if he had not been trained in bacteriology, might easily have been deceived and have accepted the author's statements as dependable evidence. To the bacteriologist, the organism was reminiscent of a common contaminator in careless work. But the author was a man of well-earned national repute and a frequent contributor to medical literature. Recognizing that the judgment of great men may be warped by overenthusiasm, the editor was, nevertheless, influenced by the author's reputation; he felt that the responsibility in this instance should rest on the author and the paper was accepted. In this case, therefore, the paramount rights of the reader were overlooked.

Recently a manuscript was submitted in which the author advanced the theory that both the cause and the cure of cancer were matters of diet. The evidence submitted, however, was not convincing and, in spite of the fact that this author also was nationally well known, the paper was returned. Shortly afterward it appeared in an eastern journal. Its publication has done incalculable harm.

Not long since, an article entitled "The Etiology and Elimination of Tuberculosis" appeared in a medical weekly. It was full of fallacy and misstatements. For instance: "The vaccine as employed against smallpox contains syphilis and is the primary cause of the white

plague"; "syphilis is the primary lesion that allows the development of tuberculosis." Further on the reader was told, as by one of authority, that syphilis is the cause of cancer. Undoubtedly the readers of the journal in question sent some emphatic protests. Instead of apologizing, the editor justified his action in publishing the article by saying: "As it was written by a physician practicing medicine we decided that it should come to light, in spite of its weird conclusions. We believed that it should be presented before the medical profession and cause a healthy discussion." This editor was not true to his readers. The two papers just referred to are being used by faddists and enemies of scientific medicine. Far more harm is done in the publication of such fallacious matter than in procrastinating with or rejecting a dozen papers offering new theories and new evidence which may be of value but which are not thoroughly convincing.

SOCIETY PAPERS

Papers read before medical societies often are not of a character to elevate the tone of periodical literature, or to add to the sum total of our knowledge of scientific medicine; as a rule, they are not well thought out or as carefully written as are those prepared especially for printing. And this is excusable. Such papers are written from a sense of duty. The author may have something that he is anxious to present to his fellows; more likely he has not, but selects his subject somewhat haphazardly. After all, the principal object of such papers, especially those read before local societies, is to bring out a discussion.

Then there is the specialist or consultant from the city who is invited by a society to visit it and to present a paper. Papers by such men are more likely to be well worked up than in the former case. The visitor is anxious to make a good impression; he will try to enlighten his hearers on the subject he presents. He thus brings profit not only to others but also to himself. Quite often, however, such papers may rightly be dubbed "pot boilers." They too are usually written for reading, not for printing.

A society paper may be ideal for the purpose for which it is written, and yet not at all suitable for publication. It may be ungrammatical, discursive or verbose, or poorly organized without sequence in argument or arrangement of the subject. And yet the author's presentation, his inflections and, above all, his personality, will carry over, not only without the audience discovering any fault, but with applause as he reads and congratulations at the end.

If the author is to be the only speaker, his anxiety will not be how briefly he can present his subject, but, rather, that he must fill the time he is expected to occupy. Brevity, conciseness, the elimination of unnecessary details, and the avoidance of branching off into unrelated and irrelevant subjects will give him no concern. He will consider as appropriate and proper the relating of unimportant incidents in his experience, as, for instance, a case report, an occasional aside, making personal allusions and using colloquial language. And he will be right. But he will not be right if he submits his article for publication without modifying it. Common courtesy compels his audience to remain and listen until he is through; but if his paper is prolix or rambling, it will have few readers; the personal equation does not enter in, and the courtesy of the listener has vanished; it is now cold type. There used to be a monthly medical journal that had this standing notice:

> Articles read before societies will not be accepted. Only those written for this journal will be printed.

I sometimes wish the rule were general. I am underestimating when I say that 10 per cent. of manuscripts have been returned because they had been prepared for reading before a society and were then submitted without revision. To a great extent it is these papers that overburden our periodical literature. A manuscript that is fit to read is sometimes fit to print, but a manuscript which is fit to print is always fit to read.

LENGTH

An occasional reason for the return of a manuscript is its length. But, like Einstein's theory as to space and time, length in this case is a matter of relativity. A paper of five hundred words may be long; one of five thousand may be short. The primary point is not length, but whether the material justifies the length. Usually manuscripts are unnecessarily long because of easily avoidable faults in construction, such as rambling, verbosity, prolixity or diffuseness.

RAMBLING, a most common fault, is the result of writing without planning. It can be overcome by organizing and by systematically laying out or plotting the subject at the beginning, as in the ordinary textbook on medicine, in which the formula is: definition, etiology, pathology, diagnosis, prognosis and treatment. Each phase of the subject is completed under its own caption. Systematic organization not only

prevents rambling—going a long way round to get to a given point—but also promotes a complete discussion, without repetition. Naturally, not all subjects lend themselves to this procedure; those of any length always do. Scientific literature is a record of facts and, therefore, style is of minor importance; but to record facts as they should be recorded, it is necessary to sort and then to arrange them in logical order. This is an important factor in style so far as medical papers are concerned.

Center heads break up solid type pages which repel the reader. They have an added advantage in aiding the author to present his subject logically and concisely. It is to be regretted that center heads are not more commonly used in medical journals.

VERBOSITY is a blemish in the writings of most of us, and one that makes reading tedious, mars diction and wastes space. This fault can be overcome easily, but in most instances, efficiently only after the paper has been written. Unless one has tried it, one will be astonished at the number of words, phrases, clauses, sentences, and, occasionally, paragraphs that can be deleted without affecting the meaning in the slightest degree. The process always improves the grammatical construction and style of expression.

Quiller-Couch, in "The Art of Writing," devotes a chapter to the use of unnecessary verbiage. Here is one of his illustrations:

> A clerk of a Board of Guardians had to record a minute relative to the burial of a pauper. The minute reads:
>
> "In the case of John Jenkins, deceased, the coffin provided was of the usual character."

Sir Arthur pulls it to pieces. First, it is superflous to tell us that Jenkins is deceased; the fact that he needs a coffin is sufficient evidence. Then, "in the case of" is superfluous, for Jenkins did not have a case; he had, and needed, only a coffin. Further, the coffin was not "of the usual character," for coffins have no character. The clerk of the Board of Guardians should have said: "John Jenkins was provided with the usual coffin."

Let us take some specimens from real life—from manuscripts submitted to *The Journal of the American Medical Association.* Here is one:

> I do not hesitate to say that in my opinion the gland in this case should not have been removed.

The first seven words are space takers; the author makes his statement and the reader cares not whether he hesitated or did not hesitate in making it. In any event, "I do not hesitate to say that" was bracketed and deleted, and the better and shorter sentence, "In my opinion the gland in this case should not have been removed" was printed. "In my opinion" might have been deleted.

This from another author:

It has been a mooted question in the minds of microbiologists whether the gonococcus possesses a capsule.

What difference there is in this case between a mooted question and one that is not mooted I do not know; "mooted" was deleted. "In the minds of microbiologists" carries the idea that only microbiologists are concerned. The sentence was improved by divesting it of unnecessary verbiage, and, when printed, it read:

It has been a question whether the gonococcus possesses a capsule.

The purist would have modified this still more and given the microbiologist a show, making it read: "Microbiologists question whether the gonococcus possesses a capsule."

This from another article describing an apparatus:

Physicians who have been using radium needles will readily appreciate the difficulties encountered in threading them.

"Who have been," "will readily" and "encountered" were deleted, and the sentence read:

Physicians using radium needles appreciate the difficulties in threading them.

PROLIXITY OR DIFFUSENESS—that is, tedious discussion of nonessential details and particularizing on trivialities—is not necessarily a fault in style or diction; it is a failure in discrimination as to what should be included. The temptation to all of us is to spread ourselves. Prolixity is especially noticeable in exhaustive analyses of previous work on the subject the author is presenting. Ambitious to make a complete and exhaustive review of the literature, he includes long abstracts of material of minor importance and irrelevant or only distantly related to his subject. Reports of postmortem examinations usually are too detailed, and contain material of no direct bearing on the subject in hand. Sometimes such a report is practically the transcript

of the stenographer's record, dictated as the examination progresses. Reports on research work and laboratory investigations often are lumbered with unnecessary details. Our German confrères, noted for their attempts at encyclopedic detail, have been inclined to elaboration and prolixity, and American physicians, especially the younger men, in the past have been prone to follow their example. Set addresses, foundation and commemorative lectures, must necessarily be long—the occasion and the time to be occupied, if not the subject, require it. Unusually long and elaborate papers cannot be avoided in treating some subjects satisfactorily. I would repeat: It is not the actual length, but whether the subject-matter justifies the length.

CASE REPORTS

The foundation of clinical medical literature is the case report, a species now becoming, for some unknown reason, almost extinct. One cause given by the editor of a Swedish medical periodical is the fact that the scientific level of our profession has risen so much in recent years that a physician hesitates to report an interesting case simply as a case report; he thinks he must make an exhaustive survey of the literature. Instead of a brief, practical report he submits an exhaustive review which few, if any, care to read, and which is unnecessary. Often a mass of detail, including unimportant, irrelevant and negative findings, is presented without regard to clearness of expression. Never a week passes that *The Journal* does not receive papers of this character. Usually if the historical review appears to be unnecessary and the case is an interesting one, the author is asked to permit the publication of the case report without the review. Clinical reports made with judgment and with the correct appreciation of relative values are always welcomed by both editor and reader.

BEGINNING

Let us now touch on one or two minor points: The beginning of an article often is the most difficult part to write; yet the difficulty is easily overcome. A good rule is, go right to the subject without preliminaries; begin in the middle, if necessary. When the paper is written, it is easy to go back and write the beginning, although nine times out of ten it will be found that this is unnecessary—the beginning has already been written. The majority of manuscripts reflect the struggle the author had in getting started. He flounders round and

writes about matters that have little to do with his theme, and, finally, after spoiling a page of manuscript, gets down to his subject. In such cases, deleting the introductory paragraphs remedies the trouble. It is well not to have chaff at the beginning; the reader may conclude there is no wheat, and skip to the next article.

TITLES

If an author desires his contribution to become a part of the literature on the subject, he must give it a name that will identify it—a title that is descriptive. Thousands of papers lie buried because their titles did not designate the subjects. Titles should be short, but inclusiveness should not be sacrificed for brevity. Often a long title may seem necessary, although usually it can be made short and clear by using a main title and a subtitle.

This was the original title of a section paper—it is a mouthful: "To Obtain Graphs Showing the Rapidity and Degree of Decrease in Temperature in the Eye and Orbit Produced by the External Application of a Given Degree of Cold over a Given Area for a Given Time, and a Numerical Expression, at Least Approximate, of the Relation of These Variables to Each Other." What can the poor indexer or cataloguer do with such a title? It became, with the author's permission, "On the Coefficient of Thermal Conductivity of Eye and Orbit Measured with Cold Applications."

Misleading titles should be avoided. "A New Chloroform Danger" was the caption of a recent manuscript. This would have been misleading, for any one looking up the literature on the dangers of anesthesia would have been attracted by the title and would have discovered that he had been misled. The title became: "Danger in Similarity of Ether and Chloroform Containers," which exactly stated the subject of the communication. First impressions are lasting: A catchy title catches readers. The title ought to be carefully thought out; it should give a clear indication of what is to come.

DIGEST AND CONCLUSIONS

A brief digest of a long article in the introductory paragraph often will stimulate some to read the article who otherwise would not. Conclusions at the end are of special value, particularly as they lend to wider publicity. Conclusions are "fat" for abstractors and for editors

who are looking for "fillers." If an author is anxious to have his conclusions reproduced by other journals, they should be rigidly condensed, yet clearly reflect his premises and deductions.

BIBLIOGRAPHIC REFERENCES

"Bibliographies," says Gould, "often are the veriest shams, appended to give a show of erudition, and their indifferences and imperfections are self-confessions of the fact." This was written twenty years ago; it applies today. Bibliographic references are of value only when the references cited (1) amplify or illuminate the subject, and (2) are accurate and complete. To include references to articles that are worthless in themselves, to those that have no bearing on the subject, and to such that duplicate or rehash papers already referred to in the bibliography is a common fault. Inaccurate and incomplete references are altogether too common. When one procures a book or journal indicated by a reference, often at much trouble and possibly expense, it is irritating to discover that one has been sent on a fool's errand—that the article wanted is not there. References to articles that have no special bearing on the subject in mind, and inaccurate and incomplete references indicate that (1) the author has been careless, that he himself has not seen the articles and hence does not know whether they are worth referring to or whether the references are correct; or (2) that he has "lifted" his references from an index or from another author. It is often possible to detect filching: if references vary in style, one giving volume and page; another, year, month and page, and still another, page, volume, month and year, it is pretty good evidence that some, if not all, of the references have been "lifted."

References should follow a definite style. Naturally, we regard the style used in the *Quarterly Cumulative Index* and in the other publications of the Association as best. It is the style used by the *Reader's Guide* (the standard cumulative index for lay publications and general literature), the *Industrial Arts Index,* which includes architectural and similar literature, the *Agricultural Index* and others. This style requires that the data shall be arranged in the following order: (1) author's surname and initials; (2) title of article; (3) name of periodical, abbreviated; (4) volume, in bold-face Arabic numerals, indicated in the manuscript by a wavy line under the numeral; (5) page; (6) month—day of month if a weekly—and (7) the year. This style is inclusive, yet brief and simple.

CHARTS; ILLUSTRATIONS

Illustrations such as charts, photographs, photomicrographs, roentgenograms, tables and diagrams are vital factors in some articles. Yet few authors seem to have any conception of the problems connected with their reproduction and printing. They send charts made on paper with the horizontal or vertical lines ruled in blue, which are lost in reproduction, since blue takes white when the engraver photographs it. Or there are many fine lines in red or some other color that photographs black, so that when the chart is reduced in size these lines run together. Often the temperature, pulse, respiration and other curves are indicated by different colors instead of different forms. Contrast should be obtained by the use of solid, broken or dotted lines, or such forms as stars or circles. The point to be emphasized is that the use of colors in charts should be avoided. Charts should be made on white paper ruled in black, and the tracings also should be black. Photographs are too often of the amateurish type, reflecting credit on neither the author nor the journal in which his article appears; and usually they do not illustrate. Tables are cumbersome and unwieldy because the author includes more columns than are required and does not know the importance of condensation in tabulating material. Scores of manuscripts have been unavailable because the illustrations were unsatisfactory.

MANUSCRIPTS

It is unwise to ignore the fact that the general appearance of a manuscript has a psychologic effect on an editor. A manuscript carelessly arranged, without pagination, with sheets of various sizes, with additions written on slips pinned or clipped to the side, with corrections made without regard to neatness or clarity, may prejudice the reader who is to pass on its merits. Even the serene and gentle editor of the *British Medical Journal* was compelled recently to give voice to his trouble: "It is common," he said, "for a surgeon to send in a bundle of sheets of paper of various sizes, fixed together with a safety pin, and containing, mixed up with the text, rough diagrams and bedside charts, perhaps sprinkled with notes and defaced by blots and corrections." Such slovenliness is inexcusable. Some men are habitually slovenly with their manuscripts, just as others are slovenly in their dress. Slovenliness has caused the return of hundreds of manuscripts which otherwise might have been accepted.

The size of the paper, while a small matter, is worth mentioning. The standard size adapted to the ordinary typewriter, the linotype machine and filing case is 8 to 8½ by 11 inches. At least 90 per cent. of the manuscripts received by *The Journal* are of this size. The other 10 per cent. vary from small note sizes to foolscap or worse.

Submitting a carbon, rather than the original, copy of a paper may have a bad effect; the editor may think the original has been sent to some other journal—at least he will think that the journal he represents has not been treated courteously. Some editors are sensitive on this point. There are practical reasons why editors prefer good, clean—the original—copy: each manuscript is read by at least one editor; then, in turn, by the copy editor, the linotype operator, and the proof reader or copy holder. Except the editor, each of these must note the spelling of every word, every punctuation mark and capital letter. The wise author, however, will retain a carbon copy and thus be able to compare it with the proof and see what, if any, liberties have been taken with his manuscript. In this manner he may discover some faults in his writing and indirectly secure criticism which will aid him in the future.

A manuscript typed in single—that is, close—space is objectionable: no matter how well written, how carefully prepared, the keen eye of the copy editor may find typographic errors, misspelled words, grammatical slips, or what not, that require interlineation. These and other corrections are made with difficulty on closely typed manuscripts. It is as easy to have a manuscript typed in double, as in single, space; it merely requires a little more paper.

The unforgivable crime is the carbon copy, single spaced. So far as our journal is concerned, such manuscripts are returned.

INCORRECT USAGE OF WORDS

As bricks are the individual elements that form the structure of the house, so words are the individual elements in the structure of an article. Words poorly chosen or wrongly used, like cracked or discolored brick, may destroy the pleasing effect of an otherwise perfect edifice. The right and wrong use of words is too large a subject to discuss here, but I want to mention a few solecisms which I regard as abominations.

CASE.—"Case" is the incidence of a disease, the totality of the symptoms and of the pathologic and other conditions; "patient" is the human being, the man himself. "The case had quite a temperature,"

"I put the case to bed," "This case was taken ill three weeks ago," "I sent the case out for a walk"—these and similar expressions are found continually in manuscripts; the error nearly always is in using "case" for "patient," seldom the reverse.

TO OPERATE.—A flagrant disregard of the rules of grammar is the deplorable misuse of the verb "to operate," which has gradually developed among a small group of American surgeons. "Operate" means, and is synonymous with, "to work"; the terms nearly always may be used interchangeably. The surgeon who would hesitate to say, "I worked this patient," says without a blush, "I operated this patient." A search of every available dictionary has failed to reveal any indication of an excuse for this abuse of the word "operate." This solecism is limited to a group that represents one in seven hundred of our population—the medical profession—and, to only a small proportion of that group—thoughtless surgeons. It is also limited to this country. American surgeons who justify themselves by saying that general usage makes correct usage should realize that "operate" is a word in general use wherever the English language is spoken; it is not limited to medicine. Men operate on the board of trade, but no one, not even our surgeons, refers to them as "operating" the board of trade. Our linotype "operators" cannot operate "on" the linotype machines; the unions will not permit it. We are compelled to employ a machinist "to operate" on the machines. Even if the term were limited to medicine good usage is not that of the majority, but that of the educated majority. The pity of it is that certain teachers in our medical schools—professors of surgery—instead of setting an example to their students in the proper use of this verb, are responsible for the spread of its improper use.

But the language of the surgeon is progressing; here is a quotation from a recent manuscript:

> It was decided that the patient should be explored with the expectation of finding an acute appendix.

The decision made, our surgeon did not hesitate; he explored the patient. Another surgeon was not so courageous: "We have contemplated having some of our inoperable cases collapsed by thoracoplasty," he says, "but have delayed." And finally, *horribile dictu*, in a manuscript for the *American Journal of Diseases of Children*, the author says: "In a case in which I obstetricated at birth." And so we "operate," "collapse," "explore," and "obstetricate" our patients.

This use of intransitive verbs in the transitive sense has no justification in the laws of grammar. Even less justification exists for transposing an ordinary common noun into a verb that does not exist. Astronomers never telescope the sky; bacteriologists never microscope their slides; but the urologist cystoscopes his patient. And in the same way, the bacteriologist who would not microscope his slides will Schick one patient, or Wassermann another. Certain rules of language and grammar are fundamental, and the canons of good writing and correct speaking govern medical, as well as other, literature. There is no place in scientific writing or speaking for such jargon or ungrammatical monstrosities.

My comments have been based chiefly on manuscripts submitted for publication in *The Journal* and in the other publications of the American Medical Association. Before printing, manuscripts pass through the copy-editing room, in which they are corrected so far as may be and prepared for the printer; hence some of the faults to which I have referred will not be found in the printed matter. "Cases" are not "sent for a walk," nor are patients "operated," "collapsed," "explored," "Schicked," or "obstetricated," in the articles as printed. Case reports are worked into fairly understandable English, crude charts are remade, and compound comminuted sentences are corrected.

But modifications by the printer should be unnecessary, not alone because the author should be responsible for his own productions, but also because modifications by another may change the meaning. Further, and particularly, every writer has a style of his own, and that style should be respected if it conforms to the ordinary rules of rhetoric and grammatical construction. Surely the percentage of physicians without educational qualifications for grammatical writing is small nowadays. The trouble is, few medical writers do their best or take the matter of authorship seriously. Any one who can write an ordinary, logical letter can write a paper acceptable to any journal, if he will take the time and trouble to do so. But writing—whether a letter or an essay—is an art. And to become proficient in any art requires work—practice. This applies to writing as much as it does to music, to painting, to sculpture and to the other arts. Perfection in any of these is reached only by practice. The fundamental principles on which good writing is based are taught in schools and colleges; yet little time is given to applying these principles by actual practice. There are schools for sculpture, painting and music, in which these arts are practiced, but

I know of no school for writing. Here and there little coteries of writers are formed for mutual assistance. I have often wondered why such groups are never formed in medical schools by students who have some ambitions for authorship and who could in this way mutually aid one another. Such an arrangement was initiated twelve or thirteen years ago in the Harvard Medical School by Dr. Burrell, professor of surgery. He described the general plan to me and later sent a proof of a circular for his students, outlining the course. How far he carried it out I do not know—not far, I fear, because of his illness, which incapacitated him for some time before his death. The plan would be ideal in hospitals in which there are a number of interns.

REVISION

I have said that writing is an art and requires practice. But the busy physician has neither the time nor the inclination to practice writing simply to improve his style. Writing is neither his vocation nor his avocation; it is a means to an end. What, then, should he do that his contributions to the literature of his profession may be creditable? The answer is: Revise, revise, and again revise his manuscript before submitting it for printing.

Few of us can write a paper of any length suitable for publication without revising and rewriting at least once. And yet I am sure that more than half the manuscripts I read have not been revised, according to the meaning of the term. Webster's definition is: "To review, to reexamine, to look over with care for corrections, as to revise a writing." This means something more than an uncritical, superficial reading of a manuscript to determine how it sounds. Such reading may satisfy the ear, but it does not satisfy the mind.

Consider how the average manuscript is written! The doctor surrounds himself with some textbooks, reprints, a few periodicals and some penciled notes, and starts to write his paper, probably in longhand. After more or less worry, and possibly some sleepless nights, he breathes a sigh of relief, thanks Heaven that is finished, and has it typewritten. He may read the typewritten copy and make one or two corrections before sending it to a medical journal; more likely, he reads it before a society and then, without any revision worthy of the name, sends it in. Not a few manuscripts submitted for publication bear evidence that the only reading given was that of the typist, and she frequently has not corrected her own misspelling. "To have a manuscript typewritten," said an editorial writer in the *British Medical*

Journal recently, "and then to send it in for publication without revision is a crime comparable to operating with unwashed hands."

Let me presume to give a little advice to those young men who are anxious that their printed productions shall be creditable: After the manuscript is typewritten and you have given it an ordinary, careful reading, to see that it sounds all right, give it not less than two critical readings. Read it first to see whether you have included all the facts or arguments you intended to include, whether their sequence is logical or whether rearrangement of certain paragraphs would be an improvement. Now have it retyped, for this will be necessary if you have made the first critical reading as it should have been made. The second critical reading is more important; while both require close application, the second requires also concentration. The object now is to improve the style, to eliminate unnecessary verbiage, and to correct slips in grammer and in construction. The matter may be forgotten; the manner of presentation is to the fore. Our copy editors go through a manuscript scarcely knowing the subject; they read it as a composition to be corrected. This is what you should do when revising your manuscript. By the time you have gone through the copy a second time, it will be so marked up that you will be compelled to have it retyped. After the two critical readings, it is quite likely that you will have become more interested and probably you will read it the third time and indicate more corrections, making it necessary again to have it retyped. What of it? The expense is small; the big thing is that you are now practicing in a most practical manner "the art of writing." And it is the only way in which the average physician can, or will, practice the art.

Sir Clifford Allbutt, in that excellent book, "Notes on the Composition of Scientific Papers," tells us that in writing an article he jots down on slips of paper ideas and facts as they come to him, which, after being arranged in logical order, form the basis for what he describes as "a hasty, first draft." "This first draft finished," Sir Clifford continues, "the work may now be regarded as half done. I usually make four drafts at least before the manuscript is finished." "After the second draft," he says, "I delete redundant words, phrases, sentences and paragraphs." On the third draft, "the composition is submitted to still closer revision; but the main work of this stage is to recast paragraphs and sentences until they run logically." Lastly, before the final revision, he lets a week at least elapse, "in order," he says, "that the final reading may be done with refreshed attention." Sir Clifford Allbutt is regarded as one of the greatest among modern English

medical writers. In view of his method of writing, is the fact surprising?

While in Oxford, last August, I saw the Osler Library—a remarkable collection of books, pamphlets and manuscripts. Osler's own annotations and an elaborate index are being completed preparatory to the transfer of the library to his alma mater, McGill, to which he bequeathed the collection. Accidentally, my attention was called to some of Sir William's manuscripts. They reveal the man. We have all regarded Osler as one of our best medical authors. His first textbook on medicine was ideal in its concise and graphic descriptions, in its compact grouping of facts in clear, simple English. As Dr. Finney, in his Osler oration, says:

> Of Dr. Osler's literary style it has been well said that his own estimate of some of the old writers may, with equal truth, be applied to him: "A rare quaintness, a love of odd conceits, and the faculty of apt illustration." There is a clarity of diction, a charm of expression, an epigrammatic style in all his writings that stamp them with a certain individuality that must leave a lasting impression on medical literature.

Some, no doubt, have envied Osler his easy command of English; but the manuscripts soon to be available in Montreal tell the true story. There were notes on paper of various kinds—backs of envelopes, for instance—evidently written on trains and at opportune moments; these form the foundation. The manuscript of the article I particularly noticed consisted of: (1) a rough outline in longhand; (2) the first typewritten copy, with interlineations, transpositions and deletions; (3) the second typewritten copy, which also had been considerably modified, and (4) the third typewritten copy that evidently had been used for printing. This final typewritten copy had three or four minor corrections.

We have all read Osler's tribute to that little word which he regarded so reverently—"work." If Sir Clifford Allbutt and Sir William Osler—the latter even in his riper years—found it necessary to revise their manuscripts three or four times, what about the rest of us?

We are leading the world in medical research, in medical progress; our profession at least equals that of any other nation in educational qualifications, both academic and professional, and in scientific attainments. Let us be an exception to the charge made by Sir James Barry, when he says: "The man of science appears to be the only man who has something to say just now, and the only man who does not know how to say it."

THE LITERARY TRADITION IN ENGLISH MEDICINE

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The main characteristics of English medicine, as distinguished from such strains as the French, the German or the Italian, are a spirit of strong, practical common sense in bedside medicine and an achievement in experimental physiology and other branches of laboratory medicine, which, often attaining the highest eminence, has been largely a matter of individual genius and effort rather than of organization, and which has always been devoted to the demonstration of a provable hypothesis rather than to the vagaries of aimless, footless and fitful speculation. As shown by the modern English writers and satirists, the shortcomings of British medicine, where apparent, have usually been associated with the somewhat artificial character of English society in the past. As enacted law is only codified custom, so social custom, in England, until recent years, has been apt to harden and stratify into phases of conservatism which were almost the equivalent of rigid law, as witness the social disabilities put on physicians and sanitarians even during the early Victorian period. At the outbreak of the European war, however, the medical profession of Great Britain was found to be in excellent form and did splendid team-work for the cause, both in the army and out of it. But vast expenditure and waste of time and money was incurred in England, as well as in the United States, through lack of forehanded organization (preparedness) at the start, as predicted in Karl Pearson's introduction to the Ninth Edition of the "Encyclopedia Britannica," This is all ancient history now, but a powerful sermon on the text:

> In ruling classes, and in social circles which put on aristocratical fashions, ideas, and especially scientific ideas, are held in sincere aversion and in simulated contempt. (Allbutt)

English medicine attained its stride progressively in Linacre, Harvey and Sydenham. It is highly significant that the first should have been a medical scholar and grammarian, the second one of the greatest of experimenters in physiology and embryology, the third the greatest clinician after Hippocrates. From Harvey to Gaskell, Lewis and Mackenzie, English physicians have always excelled in the physiology and pathology of the circulation; from the tradition of Sydenham came

Willis, Heberden, Jenner, Parkinson, Bright, Addison, Hodgkin and many others who have been among the first to describe new or hitherto undecipherable diseases, who have noted the clinical minutiae which pass silently into our textbooks, and who have invented resourceful devices in therapy, including preventive vaccination and antiseptic surgery. If we bear in mind that Harvey started modern experimental physiology, Jenner preventive inoculation against disease (do not forget his initial observation of anaphylaxis), John Hunter experimental surgery, Lister antiseptic surgery, and that ether and chloroform anesthesia was introduced by Anglo-Saxon physicians in either hemisphere, then Osler's dictum will not seem exaggerated: "The modern history of the art of medicine could almost be written in its fulness from the records of the Anglo-Saxon race."

It is the principal glory of Linacre, however, to have established a great literary tradition in English medicine, a tradition of accurate, forceful and effective writing, and it is to this tradition that Helmholtz referred when he said that the English universities excel in training young men in athletic sports, in the standards of gentility and, above all, in the use of their mother tongue.

Thomas Linacre, founder of the Royal College of Physicians, physician to the King and to many other great personages, gave up a substantial practice to take holy orders, and so became "the restorer of learning in England," one of those who, in Osler's words, "sought to break the Arabian dominion and to restore to medicine the uncorrupted spirit of Greece." Linacre's Latin translations from the original MSS. of Galen, which he found in Italy, are the most important of those made by the medical humanists of the Renaissance; his books on accidence and grammar were widely used and frequently reprinted on the Continent. He taught Greek at Oxford, wrote Latin primers for the young princes who were his pupils, and his literary reputation is well conveyed in the encomium of Erasmus: "What can be more acute, more profound or more refined than the judgment of Linacre?"

The effect of Linacre's example is at once apparent in the literary style of Harvey, who wrote well, both in Latin and English. Harvey's English letters and private memoranda, edited by Weir Mitchell, make excellent reading, and the quality of his Latin may be sensed in any good English translation of his book on the circulation. His writings are never dull and formal, but the products of an exceedingly active mind and have the stimulating effect produced by "mind in motion." That he was very much alive, even when immersed in scientific investi-

gation, is plain from the description of the Bass Rock, off the East Coast of Scotland, which occurs in his book on embryology:

> There is a small island which the Scots call the Bass Island (and speaking of this one will suffice for all), situated in the open ocean, not far from the shore, of the most abrupt and precipitous character, so that it rather resembles one huge rock or stone than an island, and indeed it is not more than a mile in circumference. The surface of this island in the months of May and June is almost completely covered with nests, eggs, and young birds, so that you can scarce find free footing anywhere; and then such is the density of the flight of the old birds above, that like a cloud they darken the sun and the sky; and such the screaming and din that you can scarce hear the voice of one who addresses you. If you turn your eyes below, and from your lofty stance and precipice regard the sea, there you perceive on all sides around an infinite variety of different kinds of sea-fowl swimming about in pursuit of their prey; the face of the ocean is very like that of a pool in the spring season, when it appears swarming with frogs; or to those sunny hills and cliffy mountains looked at from below, that are covered with numerous flocks of sheep and goats. If you sail round the island and look up, you see on every ledge and shelf, and recess, innumerable flocks of birds of almost every size and order; more numerous than the stars that appear in the unclouded moonless sky; and if you regard the flights that incessantly come and go you may imagine that it is a mighty swarm of bees you have before you. I should scarcely be credited did I name the revenue which was annually derived from the feathers, the eggs, and the old nests, which, as useful for firing, are all made objects of traffic by the proprietor; the sum he mentioned to me exceeds credibility. There was this particular feature which, as it refers to our subject, I shall mention, and also as it bears me out in my report of the multitudes of sea-fowl: the whole island appears of a brilliant white colour to those who approach it,—all the cliffs look as if they consisted of the whitest chalk; the true color of the rock, however, is dusky and black.

Of the other seventeenth century physicians, Sydenham and Willis wrote exclusively in Latin and are not specially remarkable for style. The Latin of Sydenham is, indeed, not easy to construe. The best of the eighteenth century physicians, Lettsom, Fothergill, Young, Wells, Withering, William Hunter—were facile masters of the peculiar sober-sided literary manner, of precise and formal gait, which characterized the age of periwigs, three-cornered hats, ruffles, Geneva bands, brocaded coats, small clothes, buckled shoes and gold-headed canes. Of this periwigged, slightly pompous manner, Cadogan (in his essays on gout and infant hygiene) is the most exquisite example, while such active and effective sanitarians as Sir John Pringle, Charles White and Sir George Baker are more remarkable for native fire. Heberden wrote in Latin, Jenner was but an indifferent writer of English and John Hunter, original genius that he was, shows his distinct lack of early training in an occasional pathetic groping for expression which bears out the theory of psychologists that thought itself is a function of

speech and will remain chaotic and formless until the thinker has become articulate through the exact use of words and language.

In the early nineteenth century, the literature of England was romantic in tendency, Sir Walter Scott, Byron, Coleridge, Blake, Shelley and Keats are its characteristic figures, and even Wordsworth was essentially romantic in his feeling for external nature. Something of this flavor of romance, of the feeling for strange lands and people, is apparent in the writings of John and Charles Bell, of Astley Cooper and in the large keepsake volumes devoted to the travels of Richard Bright (lower Hungary), John Bell (Italy), Thomas Hodgkin (Morocco), Patrick Russell (Aleppo) and William MacMichael (Constantinople), historian of the "Gold-Headed Cane." All the great physicians of Guy's Hospital (Bright, Addison, Hodgkin, Gull, Wilks) and of the Irish School (Stokes, Graves, Corrigan) were vigorous and effective writers. Sir Thomas Watson's treatise on practice (1843) was the acknowledged model of clear and informing literary style among the medical text books of its period.

In the second half of the nineteenth century, scientific medicine began to come into its own, and of this period Huxley is easily the topmost figure in respect of literary power and manner. Each of his sentences states a fact (a good model for all writers), no words are wasted, and the mental force behind these sentences has been likened by John Burroughs to that propelling and directing a javelin at a mark. The modest collection of aphorisms and reflections from Huxley's writings made by his widow in 1907 surpasses any other literary performance of Victorian physicians before the time of Osler and Allbutt. The writings of Darwin and Huxley have done most in the modern world to emphasize the supreme importance of scientific research, yet in this later Victorian period we find such charming books as Darwin's own travels (1860), the Horae Subsecivae (1858) of Dr. John Brown (of Rab and Marjory), Jeaffreson's "Book about Doctors" (1860), Wilks' and Bettany's History of Guy's Hospital (1892), the Medical History of Edward T. Withington (1894) and Richardson's "Disciples of Æsculapius" (1900).

English literary medicine in the twentieth century centers naturally about the work of the two Regius professors at Cambridge and Oxford. At the age of 85, Sir Clifford Allbutt, now in the plenitude of his powers, has given us the fine flower of his historical researches in "Greek Medicine in Rome" (1921), preceded by two other books of equal moment, on medieval science (1901) and on the historical rela-

tions of medicine and surgery (1905). These three books are distinguished by unrivaled knowledge, expert control of the basic sources and a literary style that is so pregnant with recondite allusion, so stimulating to thought, that one gains rather than loses on repeated reading. In "Greek Medicine in Rome" the subject is approached from a hundred different angles. No slightest fact of importance has been missed out in this wonderful book, which, to be appreciated, must be read when the mind is at its keenest. But if Allbutt writes in *oratio obliqua,* the indirection of the learned, Osler's writings are everywhere *oratio directa,* simple, direct, forward, the "literature of power," a source of inspiration to the struggling student and the overworked practitioner, and so well known to our profession that further comment is superfluous. At Oxford and in the Historical Section of the Royal Society of Medicine (organized Nov. 20, 1912), Osler gathered around him a remarkable pleiad of choice spirits—Norman Moore, D'Arcy Powell, Parkes Weber, Raymond Crawford, E. T. Withington, Charles and Dorothea Singer—and it is of the work of the latter that I desire, in conclusion, to speak.

Dr. Charles Singer, son of an English clergyman of scholarly reputation, was born at Camberwell in 1876, and after graduating in the arts from Magdalen College (Oxford), took his bachelor's degree in medicine at St. Mary's Hospital, London, in 1899 and his M.D. at Oxford in 1911. During the period preceding the European war, he held many hospital and laboratory appointments, diversified by periods of travel in Abyssinia, India, Egypt, Greece and Italy, study in Germany, and private practice in London and Oxford. His interest in medical history may be said to date from his marriage with Miss Dorothea Waley, granddaughter of the late Professor Waley of University College, London, a lady who has already done the best work to be credited to her sex in this field. Following the events of August, 1914, Dr. Singer was commissioned a captain in the Royal Army Medical Corps in November of that year, and served continuously through the war, mainly in the Levant. While on duty at Salonika, he acquired facility in modern Greek, which, in connection with previous work in the manuscript department of the British Museum, gave him (what is rare in physicians) the necessary equipment for the proper investigation of medical MSS in classical and Byzantine Greek, Latin and Anglo-Saxon. During the period of the war, his wife kept him supplied with photographic copies of medical MSS, with which he occupied what leisure he had while on military duty. After the peace, Dr. Singer was

appointed lecturer on the history of the biological sciences at Oxford and in 1920, was appointed lecturer on the history of medicine at the same university. Soon after, he was appointed lecturer on the history of medicine at University College Hospital and, in connection with this work, moved up to London.

During his Oxford period, Dr. Singer was a household friend and intimate of Sir William Osler, in whose encouragement and influence he found his best inspiration.

At London, Dr. Singer has made his courses optional to students but open to outsiders on payment of a moderate fee. He finds these courses best attended by third year students, particularly those reading for honors in biology, and has arranged special courses for medical students about to graduate. Of the ten medical schools now competing with one another in London, University College is the only one which unites a medical faculty with a complete equipment in all the other faculties. It is in fact, a university, with some 3,000 students in arts, law, science and medicine. The departments of Egyptology (under Flinders Petrie) and of physiology (under Bayliss and Starling), are said to be the best in the world, while the faculty numbers such other eminent names as Elliott Smith in anatomy, W. P. Ker in English, Platt in Greek, Gollancz in Hebrew and Karl Pearson in eugenics and biometrics. These names alone will suggest that a university so progressive, so little hampered by conservatism, can do much for the teaching of the history of science by the mere interrelation of the different faculties. Dr. Singer does not believe in making these courses compulsory, except perhaps in relation to "pass tests." It is impossible to teach men to be investigators in science. Investigators are born, not made. The best that any teacher can do is to try out different men by putting them on suitable themes, with the proper outfit of reference books, success depending on whether the pupil has it in him to profit by the stimulus of personal contact with the professor. This was the method of Carl Ludwig, who turned out between two and three hundred eminent teachers and investigators of physiology, and of whom Heidenhain said (in this relation): "Ludwig is the only physiologist who ever did anything." It was, with some reservations, the method of Sir Michael Foster at Cambridge, of Osler at Johns Hopkins, of Finlayson at Glasgow, and it is the method of Sudhoff at the Institute of Medical History at Leipzig. This seminary method has been employed with success in this country by Dock at St. Louis, W. S. Miller at Madison (Wisconsin), Riesman

at Philadelphia, and has recently been introduced at Harvard under Dr. Streeter and at Pittsburgh under Dr. Arthuthnot, Dean of the University of Pittsburgh School of Medicine. The main thing in all such courses is teaching the student how to do his own work, teaching him how to swim by throwing him into the water. "The difficulty of training a man as an investigator in medical history," Dr. Singer writes, "is of course the difficulty of his equipment. If a man comes to me who knows Arabic or Anglo-Saxon or Greek, or who has an experience among semicivilized peoples (any special equipment), I know what to do with him and can put him on something at once. But mere intelligence, is, in itself, hardly enough. I am conscious, however, that we have in this country neglected the fine field of modern medicine, and this would be the special field for the man of general intelligence." In his book on "The Future of Science," Ernest Renan argues that most writers of books on history of medicine lose their labor because they are not experts in Chinese, Arabic, Indian, and other ancient literatures. "Even supposing he knew Arabic, Chinese and Sanscrit well enough to write worthwhile monographs," he urges, "the whole life of the investigator would not suffice to make even a superficial survey of these vast and unexplored fields. It is sad to see a savant condemned to manufacture a history of Chinese medicine, merely to fill in a chapter of his book, and under the same conditions that one might write a history of Greek medicine from some faulty Arabic texts of the Middle Ages. That is why he is condemned to failure by the very table of contents (*cadre*) of his book."[1] The answer to this objection is that the best medical texts of antiquity have long since been exhumed and closely studied by experts; that investigation of ancient medicine has been of late years almost entirely in the hands of expert philologists, e. g. of Ebers and Lüring in Egyptian medicine, of Rohde, Diels, Wellmann, Ilberg and Rose in Greek and Roman medicine, of Steinschneider and Browne in Arabic medicine, of Jolly in Indian medicine, of Steinschneider and Preuss in Hebrew medicine, of Paul Haupt and the late Morris Jastrow in Assyro-Babylonian medicine; and that such excavations as those of Layard at Nineveh, Elliott Smith in Egypt, Evans in Crete, or such exhibits as that made by Sudhoff at Dresden in 1911, have taught us far more about the inwardness of ancient medicine than 90 per cent. of faulty manuscripts of uncertain value.

1. Renan, E.: L'Avenir de la Science, Paris, pp. 223-224.

The scientific and literary work of Dr. Singer comprises his medical papers, which deal mainly with diseases of the stomach and include laboratory investigations, his earlier historical papers, which are mainly devoted to histories of special subjects, e. g., contagion (1910-17), tobacco (1913), microscopy (1914-15), early treatment of gunshot wounds (1916); and his latest investigations, which are based on study of manuscript material and rise latterly into the larger atmosphere of interpretation. The fine flower of his recent work is to be found in the two volumes of "Studies on the History of Science," published at Oxford in 1917-21, and in four recent lectures and essays on Greek and medieval science (1920-21) which are based on these findings. The "Oxford Studies" consist of two large quarto volumes, made up of contributions by Singer, Withington, Crawford, and others, and more elaborately and beautifully illustrated than any other books of similar type. The two essays of Singer on St. Hildegarde and on the history of Greek science illustrate the recent trend of his work. In the first we are shown the workings of the medieval mind, as in Osborn Taylor's famous book, and realize that when the spirit of man is mainly set on the hope of heaven and the fear of hell, it is difficult to detach the mind and concentrate on objective scientific investigation, as Claude Bernard advised the scientist to do on entering a laboratory.

Supplementary to this chapter is the Oxford lecture on "English Magic and Medicine," which is most informing as to the many different elements which went to the making of medicine in the Dark Ages. Meanwhile, Mrs. Singer is at work on a reasoned catalogue of the 30,000 medieval MSS on science and medicine in England, and no less than 15,000 of these unprinted MSS are on medicine alone. Mrs. Singer's provisional classification affords some notion of what a medieval medical library was like, and how it might have been arranged. Singer's essay on the history of Greek biology, in the second volume of the "Oxford Studies," traces out in minute detail the remarkable work done by Aristotle and Theophrastus in descriptive natural history, and the effect of all this on medieval science. The beautiful full-page illustrations, mostly in colors, open up a new field in the showing up of the close observation of nature apparent on the Greek vases and in the drawings of plants by the medieval artists. The representations of the squid on Cretan and Mycenæan pottery, of the dentition of lions, of the arrangement of scales on deep sea fish, of the characteristic beak and claws of sea-eagles, on Ionian vases of the early period, are true and accurate as to identification of species, comparing favorably with

the wonderful drawings of bison in the prehistoric caves, the Assyro-Babylonian lions or the miniature paintings of birds and plants in the illuminated missals and "Books of Hours of the Middle Ages." In Singer's view, Greek science died out utterly about 400 A.D., and modern science began with the books of Vesalius and Copernicus in 1453. The real advance made in science by the medieval peoples was along such practical trends as sanitation, military surgery, the invention of printing, of gunpowder, of the mariner's compass and of spectacle lenses. All else, even internal medicine, was descriptive science, and made no such gigantic strides as are apparent in the medicine of Hippocrates, the natural history of Aristotle or the botany of Theophrastus. I would strongly advise any physician to read these two essays in the "Oxford Studies," which give us new points of view and new insight into these matters, and which have a potent interest in that these studies were fostered and encouraged by Sir William Osler, whose life-work has been a source of inspiration to us all.

SECOND REPORT TO GOVERNORS OF THE INSTITUTE OF MEDICINE OF A COMMITTEE APPOINTED TO INQUIRE INTO THE QUESTION OF NECROPSIES IN THE HOSPITALS OF CHICAGO

Following the report of the committee for 1919,[1] the committee was continued and directed to report on necropsies in the hospitals of Chicago for the year 1920. The report is as follows:

Replies to a letter and questionnaire similar to that sent out for the year 1919 were received from 40 hospitals, each having a bed capacity of fifty or more. The capacity of the reporting hospitals for 1920 was 8,460 beds; there were 161,122 admissions and 8,135 deaths. Permission necropsies were made in 872 cases and coroner's necropsies in 329 others. The latter figure does not include coroner's necropsies at Cook County Hospital. Omitting Cook County Hospital, thirty-nine reporting hospitals had 4,868 deaths in which permission necropsies were made in 556 cases, 12 per cent., an increase of ninety-four, or 19 per cent. over 1919.

In twenty hospitals, the percentage of permission necropsies was larger in 1920 than in 1919. In some the increase was striking, as for example from 8 per cent. in 1919 to 41.3 per cent. in 1920, and from 7.1 per cent. in 1919 to 31.2 per cent. in 1920; whereas nine of the reporting hospitals held no necropsies in 1919, only six reported no necropsies in 1920.

In six hospitals the percentage of permission necropsies was over 20 (52.2, 41.3, 37.1, 35.4, 31.2, 20.1), in seven from 10 to 20 per cent.; in ten from 5 to 10 per cent., and in nine from 1 to 5 per cent.

While the reports indicate that there has been an encouraging increase in the number of permission necropsies, the percentage is still far below what it should be. In several hospitals the question of necropsies has received special consideration by the staff and pathologist, with a resulting increase in necropsies, and corresponding increase in interest by the staff in improving their professional work in the hospitals.

The resulting increase of permission necropsies in hospitals where an earnest effort has been made by pathologist and staff to obtain them has confirmed this committee in the opinion expressed in its report

1 Proc. Inst. Med. of Chicago, 1920, 3, p. 150.

last year, that while prejudice and ignorance, together with religious scruples, account for much of the difficulty encountered in obtaining permission for necropsies, the alleged prejudice against necropsies is not

NECROPSIES IN CHICAGO HOSPITALS IN 1920

Name of Hospital	Beds	Patients	Deaths	Necropsies		Percentage Permission		Pathologist
				Permission	Coroner	1920	1919	
Alexian Brothers	285	3,300	270	20	40	7.4	4.9	Brother Surgius
American	125	5,000	69	2	5	2.9	12.1	J. R. Ledr
Durand	60	867	35	13	0	37.1	24.4	L. Hektoen
Augustana	200	3,935	218	10	0	4.5	3.7	A. Gallardo
Illinois Central	108	2,462	103	10	5	9.7	3.2	H. G. Wells
Chicago Fresh Air	104	282	73	5	0	6.8		
Chicago Lying-In	200	2,752	58	24	2	41.3	8.0	F. H. Falls
Chicago General	60	1,500	40	3	[illegible]	7.5		
Children's Memorial	175	2,492	222	78	..	35.4	23.1	W. G. Hibbs
Columbus Extension	75	1,578	43	3	17	6.9	....	S. Loyola
Columbus	150	3,658	52	3	13	5.7	....	C. O. Getty
Contagious Disease (municipal)	200	2,500	175	12	..	6.8		
Cook County	2,400	26,626	3,267	304	..	12.7*	8.9	F. Stangl
Frances Willard	120	3,526	81	2	5	2.4	0	
Garfield Park	60	1,500	40	0	0	0	0	W. French
German Evangelical Deaconess	68	2,300	70	0	4	0	2.0	W. H. Buhlig
Home for Destitue Crippled Children	111	996	5	..	..	0	[illegible]	
St. Anthony de Padua	200	4,236	233	3	58	1.2	4.7	F. B. Olentine
Isolation (smallpox)	50	181	1	0	0	0		
Mary Thompson	75	1,728	32	10	0	31.2	7 1	Katharine Howell
Lakeside	85	2,461	105	12	30	11.4	0	F. Hirschberg
Mercy	375	11,384	227	No definite record	12	....	18.0	
Michael Reese	459	9,093	365	41	..	10 9	9.0	O F. Schultz
North Chicago	85	2,019	51	3	1	5 8	?	Smith
Norwegian American	135	4,635	180	5	13	2 7	0	W. G Hibbs
Passavant	75	2,703	75	4	10	5.3	0	D. H. Feke
People's	40	963	45	..	..	0	0	None
Post Graduate	85	.....	56	No record	No record	....	....	E. G. Kirk
Presbyterian	425	9,300	287	150	5	52.2	48.4	B. O. Raulston
Ravenswood	42	1,536	51	10	2	19.6	13.6	J. J. Moore
St. Anne's	100	2,922	133	4	28	3.0	2.1	G. W. Wilson
St. Elizabeth's	225	4,621	247	4	21	1.6	....	L. Garness
St. Joseph's	166	4,662	199	36	5	18.1	21.4	W. H. Burmeister
St. Luke's	400	9,914	283	57	..	20.1	17.6	E. R. LeCount, Edwin Hirsch
St. Mary of Nazareth	200	4,957	282	2	14	0.7	....	J. B. Lusk
U. S. Marine	130	1,146	18	3	0	16.6	21.4	
University (West Side)	90	2,026	59	2	6	3.4	....	D. J. Royer
Washington Boulevard	85	2,595	57	4	2	7.0	8.2	H. K. Nicoll
Wesley Memorial	275	6,745	216	33	10	15.3	7.9	F. R. Zeit, J. P. Simonds
West Side	155	3,121	117	..	16	0	0	R. S. French

* Percentage of available material.

The following hospitals did not respond: Policlinic, Provident, Hahnemann, Henrotin Memorial, Park Avenue, St. Bernard, Washington Park.

so great as has been assumed, and that it is often advanced as an excuse when the real reason is indifference on the part of the staff, or lack of interest or incapacity on the part of the pathologist.

The committee is further of the opinion that indifference in the matter of necropsies often goes hand in hand with professional indifference as to the correctness of diagnosis and treatment.

RECOMMENDATION: The committee recommends that further steps be taken by the INSTITUTE OF MEDICINE to stimulate the interest in necropsies in hospitals, by urging the consideration of the subject by hospital staffs, and that the results of this survey be made available to hospitals in Chicago.

D. J. DAVIS
A. B. KANAVEL
J. P. SIMONDS
A. FRICK
ERNEST E. IRONS, Chairman

ANNOUNCEMENTS

Graham Lusk, Pasteur lecturer in 1920, and Theobald Smith, Pasteur lecturer in 1921, have been elected honorary fellows of the Institute.

At the annual meeting of the Institute, Dec. 6, 1921, Frank Billings, A. L. Kendall and Theod. Tieken were elected governors for a period of five years.

At the annual meeting of the Board of Governors, December, 1921, Frank Billings was elected president for 1922; Thomas J. Watkins, vice president; E. E. Irons, secretary; J. A. Capps, treasurer; and L. Hektoen, chairman of the board.

Elected to membership in the Institute since the last issue: A. H. Parmelee, B. O. Raulston, Katharine M. Howell, F. C. Becht, L. H. Mayers, D. N. Eisendrath, O. F. Kampmeier, E. S. Ross, and Geo. Mosher.

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THE PROCEEDINGS

of the

Institute of Medicine of Chicago

4

1922-23

CHICAGO

1923

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Green, George Willard
Greer, Jas. R.
Grulee, Clifford Groselle

*Deceased

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*Ingalls, Ephraim Fletcher
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Koch, Fred Conrad
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Kretschmer, Herman Lewis
Kuh, Sidney

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Lewis, Dean De Witt
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Marquis, George Paul
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Miller, Joseph Leggett
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Noyes, Frederick B.

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Parker, Charles A.
Parmelee, Arthur H.
Parkes, William Ross
Patrick, Hugh Talbot
Peterson, Wm. F.
Phemister, Dallas Burton
Pierce, Norval Harvey
Pietrowicz, Stephen Roman
Pilot, Isadore
Plummer, Samuel Craig
Pollock, Louis J.
Porter, John Lincoln
Portis, Milton Moses
Post, Wilber E.
Potter, Hollis Elmer
Potts, Herbert Anthony
Preble, Robert Bruce
Pusey, Brown
Pusey, William Allen

*Quine, William Edward

*Deceased

FELLOWS—Continued

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Raulston, Burrell O.
Reed, Charles Bert
Reed, Dudley, B.
Rhodes, John Edwin
Richter, Harry Mortimer
Ries, Emil
Rinder, Carl O.
Roberts, Thomas E.
Roberg, O. Theodore
Ross, Ellison L.
Rothstein, Thor
Ryerson, Edwin Warner

*Sachs, Theodore B.
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Saurenhaus, Ernst
Schmidt, Louis Ernst
Schmidt, Otto L.
Schultz, Oscar T.
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Simonds, James P.
Simpson, Elmer E.
Simpson, Frank Edward
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Sippy, Bertram Welton
Slaymaker, Samuel Robert
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Sonnenschein, Robert
Spalding, Heman
Speed, Kellogg
Stein, Irving F.
Stevenson, Alexander Francis
Stieglitz, Julius
Stillians, Arthur Wm.
Stolp, Rufus
Swan, Chas. J.
Strouse, Solomon

Tarnowsky, George de
Tatum, Arthur Laurie
Theobald, Walter
Thomas, William A.
Tice, Frederick
Tieken, Theodore
Tunnicliff, Ruth

Vaughan, Roger Throop
Volini, Camillo

Walker, Samuel Johnson
Washburn, James Murray
Watkins, Thomas James
Weaver, George Howitt
Webster, George W.
Webster, Ralph Waldo
Welker, Wm. H.
Wells, Edward Franklin
Wells, Harry Gideon
Wescott, Cassius D.
West, Olin
Wilder, William Hamlin
Willard, William G.
Williamson, Charles Spencer
Wilson, John Gordon
*Winholt, Walter Fritz
Woley, Harry P.
Woodward, William C.
Woodyatt, Rollin Turner
Wright, Frank

BENEFACTOR

Billings, Frank

HONORARY FELLOWS

Folin, Otto
Frothingham, J. T.
Loeb, Jacques
Lusk, Graham
Smith, Theobald
Vaughan, Victor

*Deceased

NON-RESIDENT FELLOWS

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Davis, Benj. F.
Doane, Philip P. S.
Dewey, Richard
Falls, Frederick H.
Gaarde, F. W.
Harvey, James Alexander
Hoskins, R. G.
Helmholtz, Henry F.
*Johnson, Frank
Mathews, Albert Prescott
Moody, Albert M.
Woodruff, Thomas A.
Webster, J. Clarence

*Deceased

ACUTE HEMATOGENOUS OSTEOMYELITIS

CLARENCE L. STARR, M.D.
TORONTO, CANADA

February 3, 1922

In view of the fact that an early diagnosis is rarely made in cases of acute osteomyelitis, and that the recognized textbook treatment of this condition in the early stage is open to question, it seems desirable that the subject should be reviewed and the experience of a large hospital clinic placed before the surgical public.

The condition which we call osteomyelitis is essentially an inflammation of all the structures of the bone, and really should be designated a periosteomyelitis. It seems incredible that an acute infection could be limited to the cancellous bone or to the periosteum, in view of the easy access and free communication between these by means of the haversian canals and para-epiphyseal line.

ANATOMIC CONSIDERATIONS

It is necessary in studying this problem to remember some of the anatomic features as they relate to bone growth and development. The circulation of an ordinary long bone, as described by Lexer, is derived from three sources:

The nutrient artery enters the shaft at about its middle and divides, sending branches to either extremity, which, after numerous divisions, end in fine capillaries near the juxta-epiphyseal line or metaphysis.

The epiphysis gets its blood supply from the cortical branches, which find their way in from the cortex along the epiphyseal line and are distributed to the whole of the epiphysis.

The cortex of the entire shaft receives its nutrition from the periosteal vessels.

The epiphysis in each long bone is, in most cases, not united by bone until early in adult life. The growth takes place on the diaphyseal side of the growing line, as can be demonstrated by an attempt to separate the epiphysis.

By forcibly tearing off the epiphysis from the shaft in the growing bone, it is seen that the separation takes place at the diaphyseal side of the epiphyseal line, and leaves an irregular series of indentations. In the child, the periosteum continued down from the shaft dips into the epiphyseal line and becomes densely adherent at this point. This condition prevents, in most cases, direct extension of infection to the joint.

ETIOLOGY

Osteomyelitis is practically always a blood-borne infection from a primary focus situated elsewhere in the body. This primary focus may be the tonsils or mouth cavity, but much more frequently some local infection of the skin, as boils or infected wounds and cellulitis. The commonest type of organism is *Staphylococcus aureus* and some strains of the streptococci.

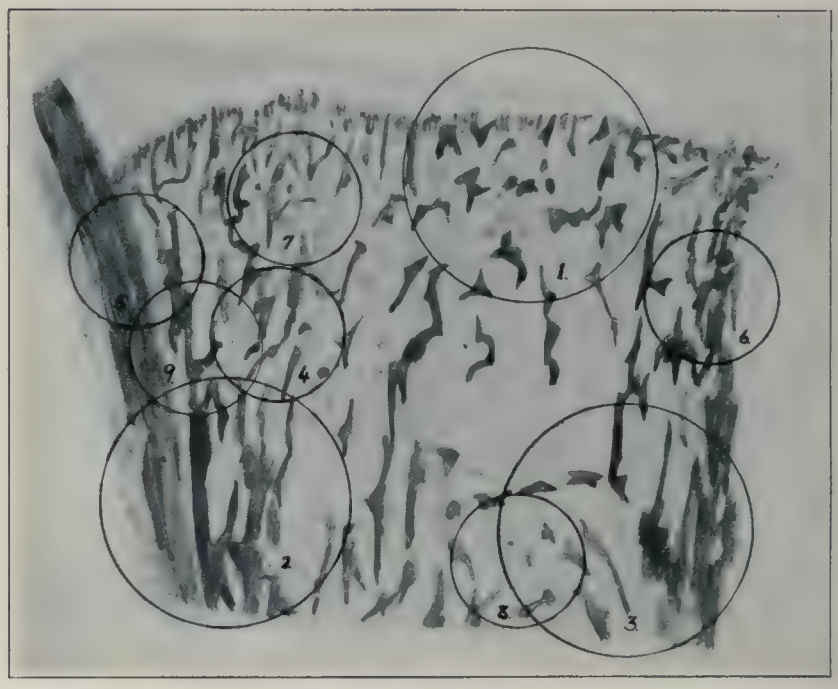

Fig. 1.—Drawing from photomicrograph, showing usual type of bone inflammation.

The blood stream infection is most frequently transient and cultures may be obtained but rarely. When the blood culture is positive and repeated, a general septicemia results, and recovery is uncommon.

The element of trauma must play a part in determining the seat of invasion. When one remembers that it is possible to wrench an epiphysis in a growing child sufficiently to produce pain or even hemorrhage into the line of growth, it is easily seen that the resistance will be low-

ered at this point, and a good culture medium provided as well. Hence it is probable that an injury may be the determining factor in localizing the site of invasion.

In our experience, the bones primarily affected are, in order of frequency, the upper end of the tibia, the lower end of the femur, the lower end of the tibia and fibula, the lower end of the humerus, the upper end of the femur, the lower end of the radius, and then the ulna, the bones of the tarsus, the crest of the ilium and scapula, in that order.

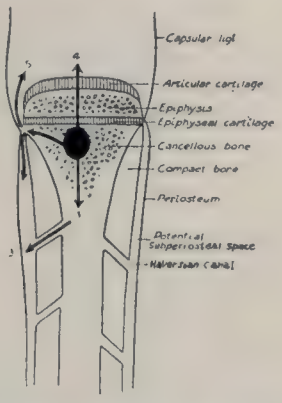

Fig. 2.—Schematic representation of a long bone, showing direction of possible spread of infection from the metaphysis (para-epiphyseal or juxta-epiphyseal region). (From Choyce, System of Surgery.)

These findings strengthen the view that trauma is a distinct factor in the disease, as it is noted that they show a greater percentage of invasion at the points most subject to injury. The lower extremity shows a higher percentage than the upper, and the neighborhood of the knee the greatest of the lower extremity.

AGE

Acute osteomyelitis is essentially a disease of childhood. It occurs at this period because the actively growing bone is less resistant to infection than adult tissue, and because trauma at the epiphysis is possible only at this age.

It is extremely rare to find osteomyelitis in the adult, aside from that due to direct injury to bone and primary infection, such as is found in compound fractures and bullet wounds. The commonest age is from 2 to 10 years.

SEX

Boys are slightly more frequently affected than girls, possibly owing to increased opportunity of injury.

PATHOLOGY

It is obvious that a true conception of the pathology of this condition must be built up, as upon this the treatment to be adopted neces-

Fig. 3. — Necropsy specimen, showing early focus of infection in the tibia.

sarily depends. Our experience does not entirely correspond to the average textbook teaching, hence it is presented in more detail than might seem essential.

The offending organisms are carried through the blood stream to reach the finer capillaries in the juxta-epiphyseal region of a long bone.

If the general resistance of the individual is lowered by ill health, and the local resistance is lowered by trauma, the infective process is started, and a small inflammatory area in the cancellous bone near the epiphyseal line results. This area shows the usual type of bone inflammation, as is illustrated by Figure 1.

The commonly accepted view is that from this focus the infection spreads with greatest rapidity through the cancellous bone to the medullary canal, and in a few brief hours may involve the whole

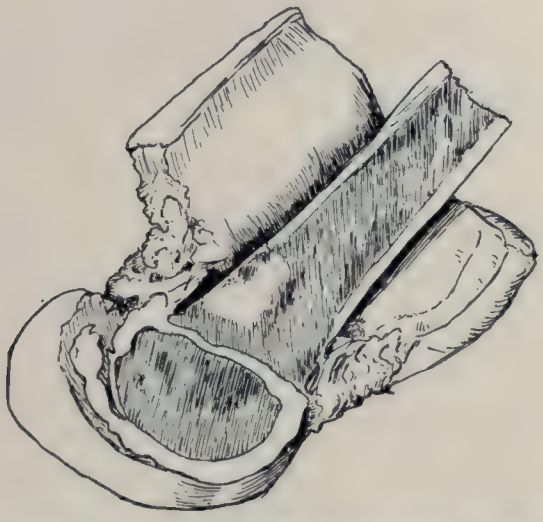

Fig. 4.—Necropsy specimen, showing early infection with inflammatory changes, marked at the periosteum and epiphyseal line.

interior of the shaft. Then it is said to spread outward through the haversian canals to the periosteum, and to undermine this structure. That it may spread downward through the epiphysis, and at times under the capsule of the joint, where it invades the joint, is also generally accepted.

Figure 2, taken from Choyce's System of Surgery, illustrates the commonly accepted view of the spread of infection. It is noted in the diagram that the chief spread is through the cancellous tissue into the medullary canal. In the text it is stated that "infection tends to spread through the cancellous tissue into the medulla, and perhaps also down under the periosteum."

In our experience, the focus of infection located in the metaphysis spreads fairly rapidly along the line of the epiphysis to reach the periosteum. Frank pus is here formed, and the infection spreads rapidly under the periosteum, stripping this structure from the bone surface. It spreads less rapidly through the cancellous tissue to the medullary canal, and the medullary canal is more frequently invaded through the haversian canals, secondarily to the periosteal infection.

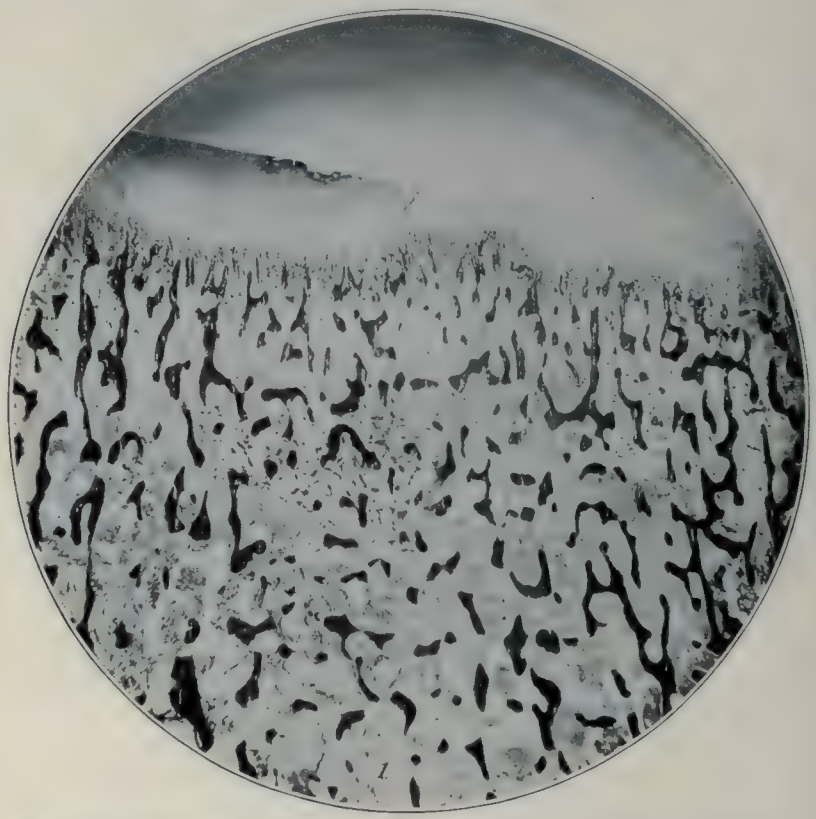

Fig. 5.—Photomicrograph of section from specimen shown in Figure 4.

This seems to be susceptible of demonstration by necropsy specimens which have been recovered from patients dying early of general septicemia, from roentgen-ray findings of the cases seen at all stages, and from animal experiments.

The tibia shown in Figure 3 was recovered at necropsy from a child, aged 2 years, who died of septicemia forty-eight hours after the onset of symptoms. It is readily noted in the specimen that the focus of infection is just above the lower epiphyseal line, and of comparatively small extent. The gross appearance shows the inflammatory area localized in this region. The microscopic section shows large colonies of cocci in the same area, with marked infiltration of the cancel-

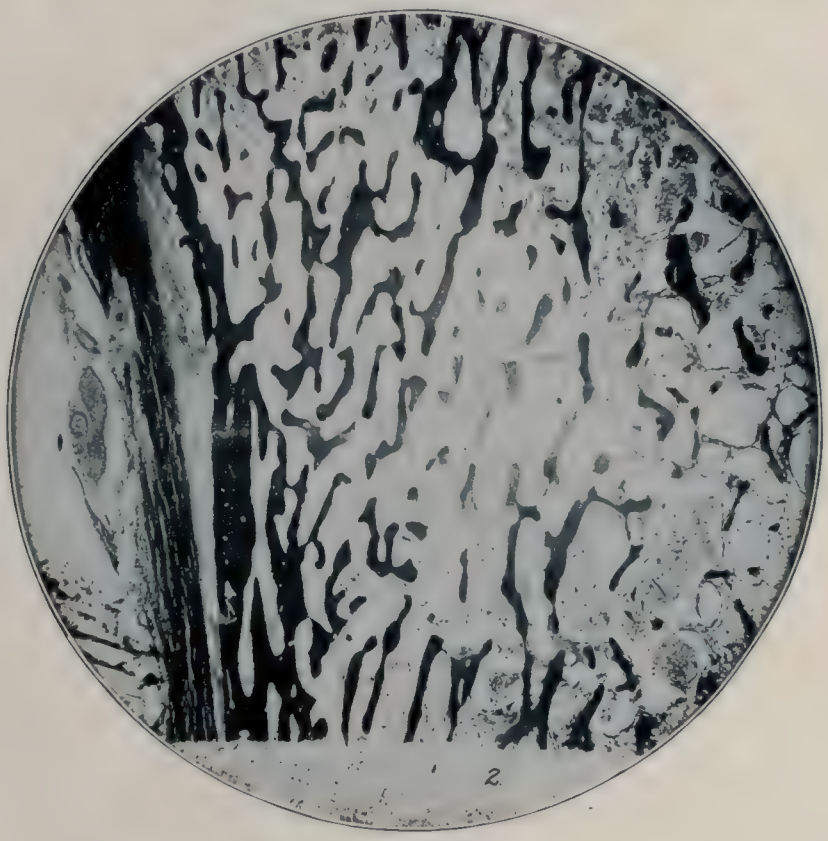

Fig. 6.—Photomicrograph of section from specimen shown in Figure 4.

lous tissue by large mononuclear leukocytes, and already some degeneration showing areas of necrosis. Higher up the shaft and in the medullary canal, there is no gross appearance of inflammation, and the sections show no organisms or evidence of inflammatory change.

The periosteum shows intensive infiltration in the neighborhood of this focus, and, as shown in the illustration, is stripped completely from one epiphysis to the other and for nearly half the circumference of the shaft. There is marked inflammatory change throughout the whole area of the stripped periosteum.

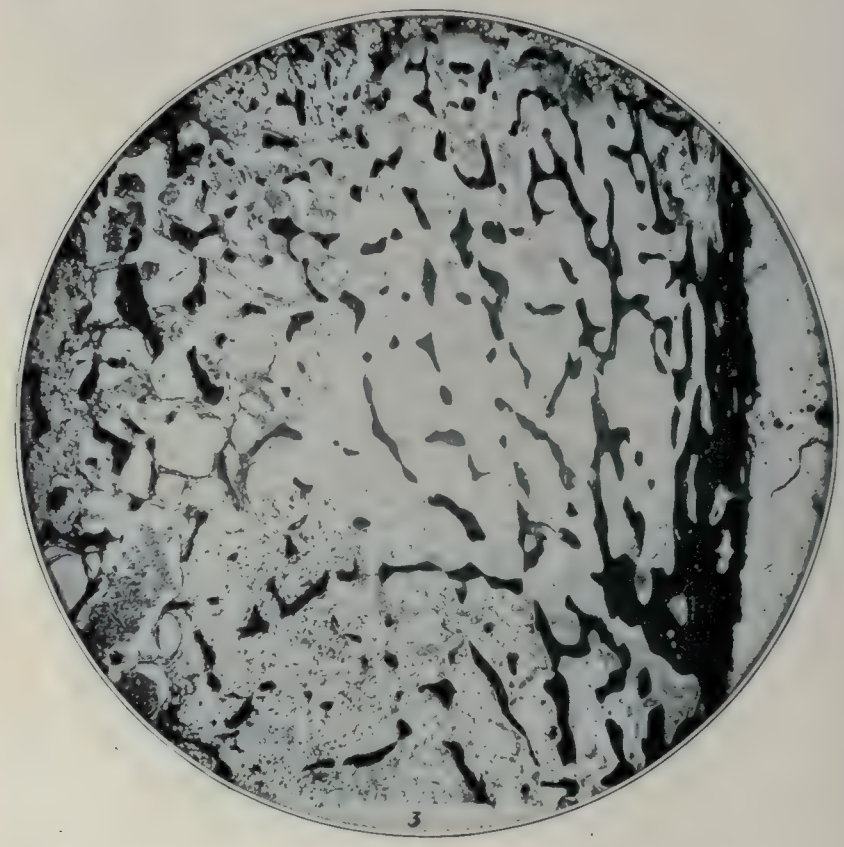

Fig. 7.—Photomicrograph of section from specimen shown in Figure 4.

The culture from this pus showed a hemolytic streptococcus, and a culture from the blood of the patient before and after death showed the same organism.

The specimen shown in Figure 4 was obtained at necropsy from an older child who died, on the third day after the onset of symptoms, of acute septicemia. This shows even more characteristically the points

brought out in Figure 3, but the periosteal stripping is not so extensive. The gross appearance shows an irregular area of gray necrosis, surrounded by dense infiltration of the cancellous tissue and an extension to the periosteum, with periosteal stripping for about 3 inches (7.6 cm.) up the shaft, and about two-thirds around the circumference of the shaft.

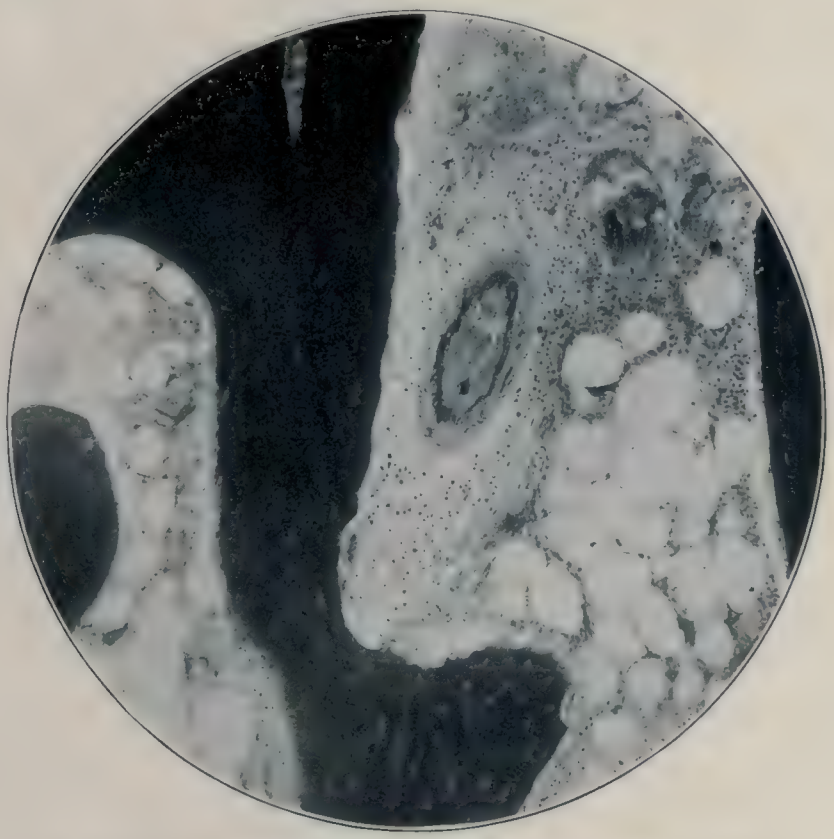

Fig. 8.—Photomicrograph of section from specimen shown in Figure 4.

Figure 1, and the microscopic sections, present the microscopic appearance of this specimen and show a marked inflammatory process in the cancellous portion of the bone, concentrated and apparently most acute at the epiphyseal line. There are large colonies of cocci, with marked infiltration of the cancellous bone with large mononuclear leu-

kocytes. Many of these have degenerated, leaving masses of necrotic material. There are large numbers of giant cells or osteoclasts in this area, which have dissolved the bone salts and left little depressions.

The inflammatory exudate extends outward, and involves the periosteum on each side, showing diffuse and focal areas of infiltration with these large mononuclear cells. In the periosteal area, there is a moderate endarteritis, and some of the lymphatics are filled with cocci. Small areas, as indicated in the illustration by rings, show varying concentration of inflammation, greatest at the epiphyseal line and along the periosteal margins, as shown in Figures 5, 6, 7, 8, 9, 10, 11 and 12.

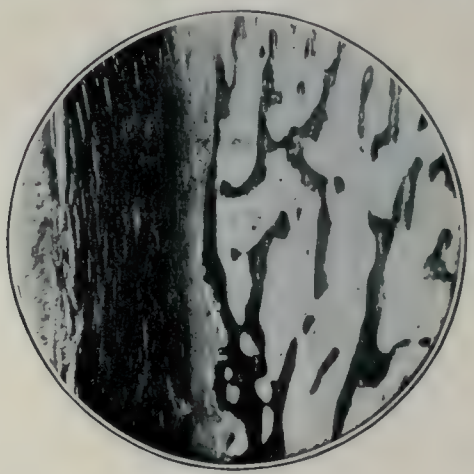

Fig. 9.—Photomicrograph of section from specimen shown in Figure 4.

Figure 13, taken at the highest point of the cancellous tissue, near the center and approximating the medullary canal, is shown free from inflammatory exudate.

ROENTGEN-RAY FINDINGS

There are several facts of importance in the study of the roentgenograms.

1. Roentgen-ray findings are always negative in the early stages. It is not until gross destruction of cancellous bone has taken place, or until new bone begins to develop as an involucrum, that the roentgenograms reveal any definite picture. This is too late to be of any diagnostic value, and it should be emphasized here that roentgen-ray findings should not be waited for in making a diagnosis.

Figure 14, taken six days after the onset, shows only a slight change in density on the diaphyseal side of the epiphysis. The physician in charge of the patient had two roentgenograms made previous to this one, and no bony change was reported. On admission, on the same day that the accompanying roentgenogram (Fig. 14) was made, incision demonstrated pus in fairly large quantity under the periosteum, firm attachment of the periosteum at the epiphyseal line, and the periosteum stripped nearly to the upper end of the shaft.

Figure 15, taken six months later, shows the amount of the destruction of the shaft.

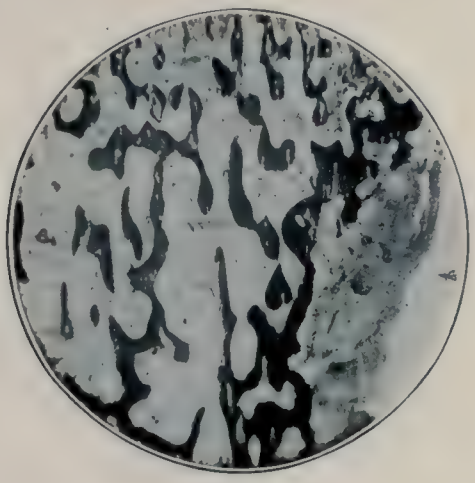

Fig. 10.—Photomicrograph of section from specimen shown in Figure 4.

2. Roentgenograms of cases of osteomyelitis which have been opened through the periosteum even moderately early, all show a fairly similar picture. The bone changes always extend farther up the shaft on the periosteal side than in the medullary area, and for the most part the periosteum is stripped higher on one side than on the other, and consequently, the destroyed part is wedge-shaped, with the base at the epiphysis and the apex on one side of the shaft.

Figure 16 shows a much greater advance of the disease along the cortical area than in the medullary area. This roentgenogram was taken one month after onset, and the physician had evacuated pus from under the periosteum on the seventh day. The relief of tension under

the periosteum had at once limited the extension of the disease both in the medullary area and under the periosteum.

3. Roentgenograms of still later cases, when the tension of pus under the periosteum has not been relieved, show a characteristic "spotty" infection, as if the organisms had been poured through the cortex at various places. This is well shown in Figure 15, where the periosteum was not incised until nearly entirely stripped.

Figure 17 was taken six months after the onset, during which time no treatment had been instituted, but the abscess had been allowed to burst. This also shows the spotty character of the infected bone, as well as areas of shaft and medulla which appear quite normal.

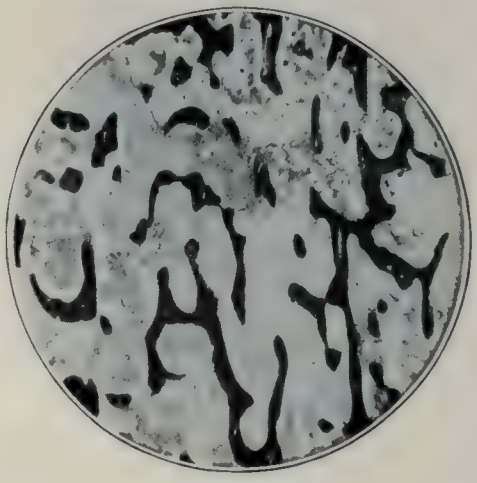

Fig. 11.—Photomicrograph of section from specimen shown in Figure 4.

ANIMAL EXPERIMENTATION

At first in our experimental work, which has been carried on largely by Dr. R. I. Harris, we found great difficulty in producing osteomyelitis in the dog, even with staphylococci or streptococci of known virulence in man. Therefore, our earlier demonstrations were chemically produced with croton oil, sealed with agar and planted in the bone near the epiphysis, as employed by Bancroft and Clarke. These experiments succeeded in demonstrating the process of destruction and sequestration, but were not satisfactory as proof of the spread

of infection. It was found that by tying off the appendix and its mesentery in the dog a general peritonitis is produced. The organisms from this infection if injected into a nutrient artery or into the traumatized metaphysis will produce an acute osteomyelitis in the growing dog. In every case the dog has died within forty-eight hours, but the osteomyelitis is characteristic. The periosteum is rapidly stripped, with findings similar to the sections shown.

No dogs lived long enough to allow the production of later changes and sequestration; but it is quite apparent that the early changes are in the nature of an inflammatory condition along the epiphyseal line, with rapid extension to the cortex, and frank pus under the periosteum.

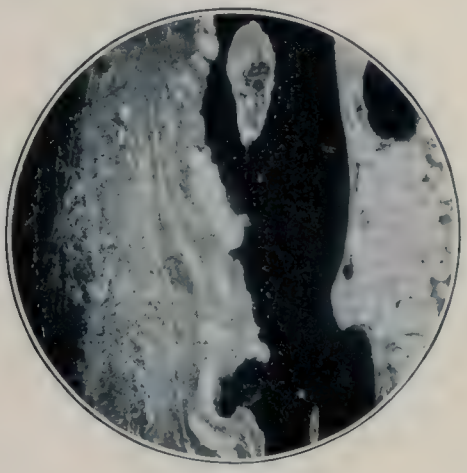

Fig. 12.—Photomicrograph of section from specimen shown in Figure 4.

From the foregoing presentation of early pathologic changes shown from human necropsy specimens, from the roentgen-ray findings of cases of longer standing, and some of late cases, and from the correspondence of the findings in the animal experiments, it seems reasonable to conclude that, for the most part, infection starts in the metaphysis or diaphyseal side of the epiphyseal line; that it extends most easily along the epiphyseal line to the cortex and the periosteum; that it readily and early strips the periosteum, with increasing tension as more pus is formed; that with increased tension the infection

probably spreads backward through the haversian canals at various levels, and invades the medulla from the cortex, giving this spotty character to the shaft infection.

One should feel that the firm attachment of the periosteum is a safeguard to direct extension to the joint by this route. It is also most unlikely that infection will travel through the epiphysis and articular cartilage direct to the joint.

The neighboring joint is, no doubt, involved in a small number of cases; but I am beginning to believe that it is more often infected secondary to operation, than as a result of primary extension.

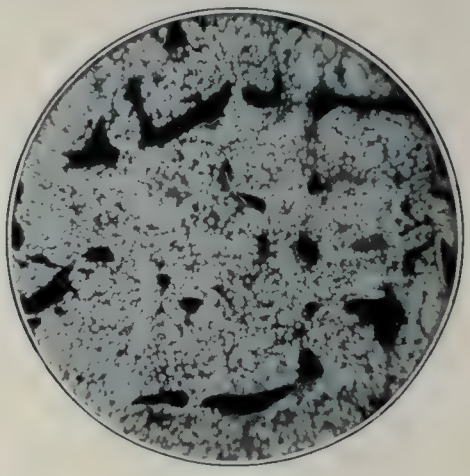

Fig. 13. — Photomicrograph of section of cancellous bone near medullary canal (Fig. 4).

That a serous synovitis occurs from adjacent infection, and consequent hyperemia of the synovial membrane, is unquestioned; but these will usually subside without aspiration or incision.

The changes occurring in the later stages are so well known that they need no elaboration. The formation of a bony wall or involucrum on the under surface of the periosteum, the sinuses passing through this bony covering, the gradual separation of the necrotic area or sequestrum by a layer of granulation tissue forming between the living and dead areas, are conditions which are well described in most text-books.

Fig. 14. — Roentgenogram taken on the sixth day after onset, showing no bony change.

SIGNS AND SYMPTOMS

Following a fall or moderate injury, there is complaint of pain, severe, of sudden onset, and located in the neighborhood of a joint. This may be preceded a few days by a sore throat or a discharging ear, or some other primary source of infection may be found. Accompanying the pain, there will be tenderness over a limited area, and most extreme at that point. There will be signs of toxemia, headache, dry tongue, sometimes vomiting, with a pulse rate as high as 120 or 130, a temperature of 103 or 104 F., and a marked leukocytosis as high as 25,000 or 30,000. If left alone, later symptoms of redness, swelling, and marked edema develop. With these there is a corresponding increase in the toxic symptoms.

DIAGNOSIS

The diagnosis must be made on the signs present. Severe pain in the neighborhood of a joint, with a spot of extreme tenderness, in a growing child is extremely significant. If it is accompanied by high fever and rapid pulse, with high blood count, the diagnosis is moderately certain.

It is so essential that an early diagnosis be made, that one should be constantly on guard. The roentgen ray is of no assistance in early diagnosis. Valuable time is consumed, which means more and more bone destruction. Salicylates should not be administered if time is lost thereby.

In rheumatism the onset is not usually so severe, nor the pain so excruciating. There is no sharp point of localized tenderness, and the pain is articular, not in the neighborhood of the joint. There is almost immediate swelling of the joint in rheumatism.

An infectious arthritis is sometimes confusing; but the joint manifestations are usually sufficient to differentiate this condition. There is muscle spasm, limited movement of the joint, and early swelling of the synovial pouch. In osteomyelitis the joint is usually free of swelling, and movements are free if gently attempted. Do not wait for signs of swelling, redness and edema, as these are rather later signs. Of course, if these are present when the patient is first seen, they render the diagnosis still more certain.

TREATMENT

The diagnosis being made early, treatment should consist of incision over the area of greater tenderness, through the skin, subcutaneous

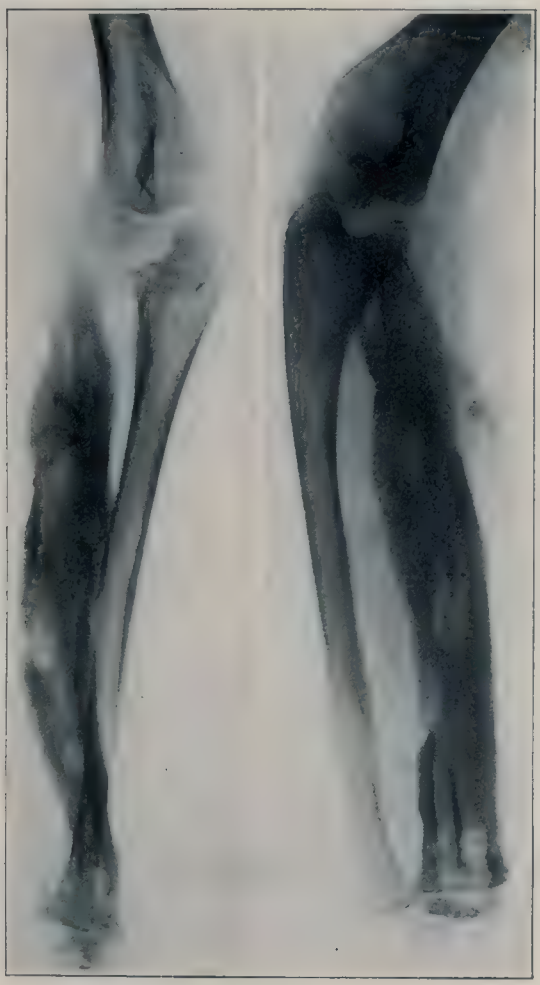

Fig. 15.—Roentgenogram of same case as that shown in Figure 14, six months later.

tissue and periosteum to the bone. Care should be exercised to keep the incision clearly on the diaphyseal side of the epiphysis to preserve the periosteal attachment to the epiphyseal line. This safeguards to a large extent the possibility of extension to the joint.

If frank pus is encountered, our experience shows that this incision is sufficient, if a drain is kept in for a time. If no gross pus is encountered, the periosteum is stripped for a short distance on either side of the incision, to be sure that the incision is not in the wrong place.

If still no frank pus is seen, a series of possibly three drill holes is made from the cortex, obliquely downward toward the epiphyseal line. These are about one fourth of an inch (6.4 mm.) apart up the cortex, and extend at least into the center of the shaft at the epiphyseal line, as shown in the diagram (Fig. 18).

Cultures from the débris removed from these drill holes always show infective organisms, even though free pus is not obtained. These establish clear lines of least resistance, and within twenty-four hours pus is draining freely.

In no case have we opened the medullary canal, and in all cases the infected bone seems limited to the area present at the time of establishment of drainage.

The treatment usually advocated, of trephining an opening into the medullary canal, 2½ inches (6.4 cm.) or more up the shaft, seems, in the light of our experience, to be pernicious.

If the periosteum is opened and holes drilled into the shaft at the metaphysis (Fig. 18), one can hope to relieve the symptoms and prevent necrosis sufficient to produce sequestration. Even if free pus has stripped the periosteum, if it is confined to a small area, regeneration of the necrotic area may take place without sequestration. The subjoined case illustrates this type.

A. B., a boy, aged 12 years (Fig. 19), had sore throat, headache and cervical adenitis, one week before onset of symptoms in the arm. Two days before admission he had pain, which increased in severity just above the left elbow. Slight swelling was noted the day before admission.

On admission he had pain just above the left elbow, some swelling and redness over the inner aspect of the humerus, with pitting on pressure and exquisite tenderness. Movement at the elbow was nearly complete in range, and only painful when the arm was extended to its extreme length. The temperature was 103 F.; the pulse, 150; respirations, 30; white blood cells, 24,000; polymorphonuclear leukocytes, 98 per cent.

A free incision over the inner side of the lower end of the humerus, above the epiphyseal line, opened a cavity containing ½ ounce (15 c.c.) of pus. Culture from this pus showed a hemolytic streptococcus. A blood culture taken at the same time was sterile.

Fig. 16.—Usual appearance of untreated bone.

The boy had a rapid convalescence, and was discharged from the hospital at the end of three weeks, with the wound healed. It has remained healed ever since, now one year.

Figure 20, a roentgenogram taken four months later, shows some periosteal thickening and no cancellous tissue change.

Fig. 17.—Roentgenogram taken at a late stage, showing "spotty" infection

In the series of patients under treatment there are six that have been similarly treated; and the wounds have healed in three or four weeks without a sequestrum being formed. There are also three patients with positive blood cultures on repeated examination, who recovered with greater or less sequestration of necrotic bone.

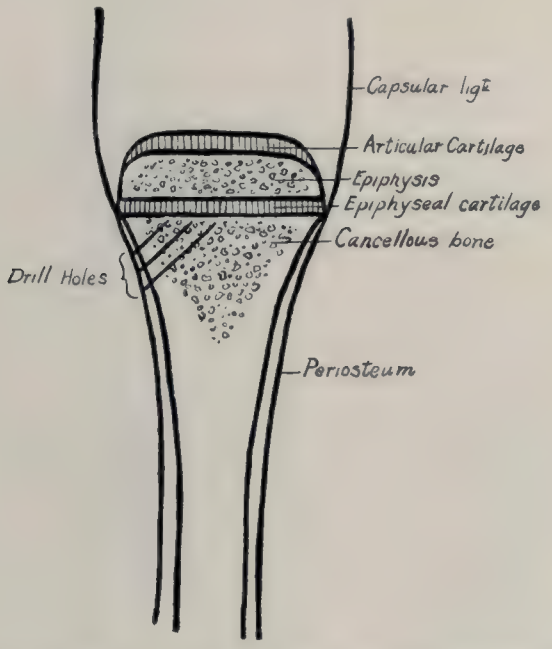

Fig. 18.—Series of drill holes from cortex to epiphyseal line.

In the later stages the plan of treatment adopted is this: After efficient drainage has been established, operation is delayed until the sequestrum is separated. Then a channel sufficiently large to remove the sequestrum is chiseled through the involucrum; the cavity is gently curetted until it is free of dirty granulations; the cavity is sponged with iodin, and packed tightly for forty-eight hours with iodoform gauze after which all packing and drains are removed. If the cavity left is too large to fill easily by granulation, the edges are made saucer-shaped, or flattened, to permit the soft tissues and periosteum to fall in and obliterate it.

Fig. 19.—Arm of patient on admission.

It is rare to find in hematogenous osteomyelitis the large central cavities that one finds in osteomyelitis near the extremity of a long bone following a gunshot wound, which can best be obliterated by a transplanted muscle flap.

Fig. 20.—Arm of patient, four months later.

The practice of attempting to chisel away necrotic bone before it has delimited itself is to be condemned, as it is impossible to determine where the necrotic bone ends and where the living bone begins. Living bone is thus either taken away or necrotic bone left.

In the operation of making a depressed or saucer-shaped cavity the periosteum should not be widely separated from the living bone, as this is likely to interfere with the circulation of the bone tissue immediately underneath, which may also have its endosteal circulation cut off. This would, of course, make a new necrotic area and subsequent sequestrum.

The blind curetting of a bone cavity where there may or may not be a sequestrum is not a procedure which is likely to produce any beneficial results. In our experience the sequestrotomy should be performed in a bloodless field, using a tourniquet wherever it can be safely used.

Ill-considered and incomplete operations in the latter stage are largely responsible for the fact that in so many of these bone cases discharging sinuses continue for years, and the patients are subjected to operations without number.

DISCUSSION

ARTHUR DEAN BEVAN: We were for many years altogether too radical in our handling of these cases and have done damage by too much traumatism at the time of the early operation in acute osteomyelitis. The experience of Dr. Starr is the experience of the Heidelberg Clinic in the last ten or fifteen years. The difference in the result between the radical procedure in osteomyelitis and the more conservative procedures has shown that the conservative procedures have saved about twice as many lives. Many of us have felt that we should expose the focus and thoroughly eradicate it. We frequently have in the same case within a period of a week or ten days or two weeks this sort of experience: A primary focus in the tibia, which is pretty extensive and acute and followed by destructive bone changes; within a week there is a secondary point of infection in the lower end of the opposite femur and within a few days another lesion, let us say in the elbow joint and the fading in severity from the first severe infection as compared with the second and third is often noticeable. Now when we do a radical operation it is with the conception that we are going to clean out the disease with the removal of this focus as we do when we remove an infected appendix, and it is a wrong conception of this disease because often the patient will have his secondary focus, his tertiary focus or even a fourth or a large number of foci. If we obtain good drainage of the primary focus with slight traumatism, we are doing much more for our patient than we can if we attempt the old, radical operations.

Many of our colleagues are doing mastoid work who do not understand the principles of general surgery as they should and they are overdoing much the operation in acute mastoiditis just exactly as many of us have overdone the operation for osteomyelitis in other fields. There is no doubt in my mind that in acute mastoiditis we should be governed by exactly the same principles that Dr. Starr has laid down, that we are to expose the field and that we are to obtain drainage with the least amount of trauma, and if we do this we shall save more lives than are saved in these very radical operations in the acute stage of the infection and we shall have fewer sinus thromboses and brain abscesses.

A. J. OCHSNER: The operation that Dr. Starr proposes in acute osteomyelitis changes the direction of the lymph stream. The moment you have laid open the periosteum there can be no further backing up of infectious material as shown in the diagram, and the amount of destruction that has taken place is all that will take place. I should like to emphasize the importance of locating the origin of the infection and to advise invariably to eliminate the origin of the infection when this is possible.

C. L. STARR (closing): I came down thinking I was going to drop a bomb into things and that I would probably go home without my scalp. I am glad that Dr. Bevan feels as he does regarding the conservative treatment and I hope his influence will be sufficient to change the character of our textbook teaching, as mine has not been. You cannot pick up a textbook in this country without finding this statement, that when the infection is not found under the periosteum, we must trephine into the medullary canal. In some they go so far as to say it should be laid open from one end to the other. Our students are learning that method. If we are going to relieve the condition we must have early diagnosis and the early diagnosis must be made from the symptoms before there are obvious signs. Look for the lesion in the bone and having located that, get sufficient drainage, thus you will cure the case without sequestration. I think that is the thing to look forward to. Another point, in some textbooks the diagrams are diabolical. You will see in a number of books a focus in the center of the shaft. No man here ever saw acute osteomyelitis in the center of the shaft. That diagram makes an impression on your students and it is hard to eradicate it. Right next to that diagram you will probably have an x-ray plate showing the true location of the osteomyelitis, in the region of the epiphysis. Such things should be eradicated, so that we may have some foundation for our students for real work. I think that is the factor we have to consider in all our teaching. It is very difficult to fight against tradition.

DR. WENDELL C. PHILLIPS, New York: I would like to ask, whether in what we call abscess of the temporal bone it is true that to merely trephine a hole into the temporal bone and drain it is going to bring as good a result as a complete mastoid operation.

A. D. BEVAN: I have in mind the conception that Sir William Macewen held regarding acute mastoiditis of simply opening the mastoid cells and mastoid antrum. I mean in the very acute cases. I believe this plan is much safer than doing a radical operation in the face of an acute infection.

DR. WENDELL C. PHILLIPS, New York: I cannot refrain from challenging the statement of Dr. Bevan regarding purulent middle ear infection involving the mastoid bone. This audience should not be allowed to go out with the impression that merely to drill a hole in the cortex of the temporal bone and let the pus drain is better than to do what we otologists have found is the best, namely a complete and thorough eradication of the disease in the temporal bone, because this procedure gives a more complete and rapid healing. By so doing our statistics show that we have far less complications and that complications like lateral sinus thrombosis are much more liable to occur after incomplete operations. Furthermore, the middle ear suppuration is apt to be prolonged after incomplete operations. All otologists are called on to reoperate and often to do the radical mastoid operation on these halfdone operations. With rare exceptions acute mastoiditis is not to be considered as osteomyelitis of the mastoid.

SURGICAL VERSUS MEDICAL TREATMENT OF GASTRIC AND DUODENAL ULCER

ARTHUR DEAN BEVAN

February 3, 1922

During the last ten years or more I have had the opportunity of making, with my medical colleagues at the Presbyterian Hospital, a combined study from both the medical and surgical point of view of the subject of peptic ulcer. I believe that we have approached this matter with an open mind and have attempted in this clinical research first, to establish the relationship between the clinical picture and the pathologic anatomy, and second, to determine the value of both the medical and the surgical treatment and the indications for each. During this period of ten years, of course, similar researches have been made in a large number of clinics, both in this country and abroad; notably in the Mayo Clinic in Rochester, the work of the Leeds group in England headed by Moynihan, the work of von Eiselsberg and his assistants, Haberer and Clairmont, and the work of Schmieden, who was formerly with Bier and who now has a chair of surgery at the new University at Frankfurt, and, of course, the work of many others.

I shall attempt to summarize briefly the results of my experience with this problem. In the first place, I think it might be well to discuss the present status of our knowledge of the etiology of peptic ulcer. Peptic ulcer is a lesion in which a number of factors play an important part in causation; but, of course, that is true of almost all lesions. Take, for instance, such a simple lesion as a furuncle on the back of a man's neck. I have for years taught my students that here we had at least three causative factors and have expressed the matter by algebraic equation: $X + Y + Z =$ furuncle. In this equation X is the essential germ cause, usually Staphylococcus aureus; Y is the small abrasion produced usually by a rough collar which furnishes the atrium of infection; Z is the general lowered resistance of the person that permits the growth of the organism in his tissues; these three factors combined produce the resulting boil.

I think the peptic ulcer is probably a more complicated condition than the simple boil, and that we have at least three and probably more factors in its causation; if we expressed these in the same algebraic

way we would have X + Y + Z = peptic ulcer. I am rather inclined to put the X in this equation as the gastric juice with its power of digesting devitalized tissue. I place this first because it is the characteristic factor of peptic ulcer which does not occur in the absence of gastric juice; Y is an area of lowered local resistance resulting usually from some injury or disease of the blood vessels of the mucous membrane interfering with the blood supply of a small area of tissue and so lowering its vitality that the gastric juice can destroy and digest it; Z is again the lowered general resisting power of the person, and I think in this case probably a rather complex picture as this lowered resisting power may be due to a number of quite different causes.

First, anemia is undoubtedly one of the conditions lowering the resisting power of the patient. General poor nutrition is an important factor. This has been well demonstrated in the last war when the hunger blockade of the Central European countries was followed by an enormous increase in peptic ulcer, due principally, of course, to the lack of proper food and to food often that is difficult to digest. Another factor which lowers the resistance of the person and plays an important part in the production of peptic ulcer is the increased nervousness of the patient. Nervous strain "worry" is recognized by a number of investigators as being one of the important factors in the development of peptic ulcer. This may produce its effects in several ways, increasing possibly the high acid content of the gastric juice, and possibly by producing pyloric spasms, or possibly by producing lowered resistance against the action of gastric juice by impairment of proper nerve function, although these last suggestions are of course purely theoretical. I think we can safely say that all of these three factors—the X + Y + Z —which I have described, play important parts in the production of peptic ulcer.

There has been a good deal of investigation of late years directed toward demonstrating that focal infections, such as in the teeth, tonsils, an infected appendix or infected gallbladder, might be the causes of peptic ulcer by producing hematogenous septic infarcts of areas of the mucous membrane of the stomach. Rosenow has particularly called our attention to this point, and there can be no doubt that infections occur in which we have the picture of an acute ulcer of the stomach or duodenum which results from a hematogenous infection of septic embolism of a vessel of the mucous membranes of the stomach, from a focus of infection such as in the tonsils or teeth or from an extensive

area of skin infection following a burn. My own impression is that these acute cases usually recur promptly, or if they are very serious may result fatally of course; but I believe that it is not the ordinary common cause of peptic ulcer of the stomach and duodenum which we see clinically, and that the infection from pus organisms plays a minor rôle in the causation and the persistence of peptic ulcer.

I shall now present briefly my conception of the symptoms of peptic ulcer, especially the essential and common symptom of stomach distress. The sensations experienced by the patient with peptic ulcer may be described as a sensation of discomfort or distress, or of actual pain. We surgeons who operate today, frequently under local anesthesia, on abdominal viscera recognize the fact that we can handle the stomach and duodenum with little or no distress to the patient. We can sew the stomach and intestines together as in a gastro-enterostomy without any sensation. We can take a cautery and burn off the end of the stomach or duodenum without any sensation, and we sometimes wonder why an ulcer in the duodenum or in the stomach produces pain and how it produces pain. We know that if in performing an operation under local anesthesia we pull on the viscera we can produce great pain. We know too that in the abdominal cavity the most common cause of pain is distention of some viscus, as is clearly shown in the great pain resulting from obstruction of the cystic duct in gallstone colic, or the great pain resulting from obstruction of the ureter in kidney-stone colic, or the great pain resulting from the obstruction of the bowel in ileus. In these cases we can quite clearly see and it can be demonstrated experimentally and clinically that it is the intravisceral tension which produces the pain. We know too that the tissues that are the site of an inflammatory process are much more painful than the normal tissues in the body cavity.

Pain, as I have studied it in peptic ulcer, occurs under three conditions: First, when there is an intravisceral tension due to the distention of the stomach or the bowel with gas and food, and associated often with a spasm preventing the normal emptying of these structures; second, pain which seems to be due to the irritation of the gastric juice on the raw surfaces of the ulcer, the so-called chemical pain; and there is a third kind of pain which undoubtedly is due to the lighting up of an acute inflammatory process in and about the ulcer itself. This sort of pain is apt to produce a picture in a case of duodenal ulcer resembling closely a gallstone attack. I have been able to unravel a number

of cases in which, because the character of the pain so closely simulated gallstone colic, we had made that clinical diagnosis before operation, and in which at operation I have found no lesion of the gallbladder but an inflamed and often a penetrating ulcer, usually either in the duodenum or close to the lessor curvature.

I can understand quite well the stomach and duodenal pain which results from intravisceral tension and the pain which results from an acute inflammatory process developing in and about the ulcer. In the light of the fact that we can crush a part of the stomach or the duodenum or cut it off or destroy it with a cautery without producing any sensations to the patient, it is difficult to understand how gastric juice poured over the raw surface of an ulcer can produce pain, unless we accept the theory that in this pathologic condition of ulcer the tissues are more sensitive than under normal conditions; this, I take it, is the fair and logical explanation of the facts. I am quite willing to accept the generally accepted belief that the ordinary pain of peptic ulcer is due to the pouring over the raw surface of acid gastric juice with a high free hydrochloric acid content, and I think we are compelled to accept this point of view by the results, which we can so constantly observe, of the neutralizing of free hydrochloric acid with alkalis, with the resulting cessation and disappearance of the pain. I wish, however, to say that I believe that intravisceral tension plays a definite and important part in the distress and pain of peptic ulcer, as it does in almost all painful conditions of the abdominal viscera. I believe that this phase of peptic ulcer deserves special study and that when this problem is solved we shall have learned that here, as in almost all painful abdominal lesions, intravisceral tension plays an essential part.

I shall next present to you my conception of the healing of these ulcers. I want to make a parallel, as I have done in my own study of this trouble, between the ordinary varicose ulcer of the leg and peptic ulcer. We can study the healing process of an ordinary varicose ulcer and watch the process directly under our eye from day to day and see what happens in the healing of an ordinary varicose ulcer. First, let me again apply our algebraic equation that $X + Y + Z =$ varicose ulcer. In this algebraic equation the X, the essential and characteristic factor in the etiology, is the obstruction of the return circulation; Y is usually some slight traumatism of the skin—barking the skin from some little injury. This slight injury becomes the starting point of an ulcer, sometimes of considerable size. Instead of healing,

the tissues about the injury break down and the ulcer grows in size; Z is the general resisting power of the individual again, and this is modified by poor nutrition, poor hygienic surroundings and general constitutional disease. If one makes a culture of the secretions of the varicose ulcer, he will have no difficulty in demonstrating pus organisms of various kinds and often saprophytic organisms. I believe, however, that these organisms do not play an important part, either in the production of the ulcer or in preventing the healing of the wound. Of course, at times a varicose ulcer becomes acutely infected and inflamed. I would draw, therefore, a close parellel between the varicose ulcer and the peptic ulcer so far as pus organisms are concerned; that is, that they are present in both, that they are, however, as a rule simply an incident, and that they may occasionally be the cause of the lighting up of an acute infection, but that they are not the essential cause of the ulcer.

Now let us examine the natural history and the healing of a varicose ulcer. I think I can speak on this subject with some authority as I have watched carefully a large number of these cases. Keeping in mind the X and Y and Z which equal varicose ulcer, if we place the patient at absolute rest in bed in a recumbent position and elevate the affected limb, we do away for the time being with the X, the most essential factor in the production and maintenance of varicose ulcer; that is, the interference with the return circulation. If we do this only without attempting to do anything else, as a rule in a limited period (10 days to 2 weeks or more) the ordinary varicose ulcer will heal. In the healing process the bacteria which are on the surface gradually disappear and granulations become healthier, and with the complete epidermization of the ulcer the bacteria disappear entirely. If the general condition of the patient is bad, if the patient is anemic, run-down, undernourished, of course improved hygiene, better food, fresh air, cleanliness and attention to proper elimination are important in improving the general condition of the patient, and under this improved general condition wound healing is more rapid.

If there is a combined condition, such as varicose ulcer plus syphilis, antispecific treatment is of definite value. In other words, the history of an ordinary varicose ulcer is that when we remove the essential cause and contributing causes and place the patient and the part involved in the best possible condition for healing, especially when we remove

the essential cause, the interference with the return circulation, wound healing as a rule occurs promptly.

There are, however, some exceptions to this rule. The old-time surgeons recognized the existence of some of these old ulcers of the leg of a certain type which they called "callous ulcers." If you examine one of these, you will find a rim of dense scar tissue around the ulcer and in crater-like depression of the ulcer itself. In these callous ulcers wound healing is very slow and sometimes almost impossible to obtain under the ordinary elevation of the limb, rest and improved general condition of the patient, which is so efficient in varicose ulcer of the ordinary type. Old-time surgeons understood this problem very well, and in order to heal one of these ulcers they would dissect out the hard indurated callous margin of the ulcer and the base of the ulcer itself, then place the patient in a recumbent position and treat the ulcer as the varicose ulcer of the ordinary type and obtain healing.

There is a third type which one might mention in continuing this parallel between the varicose and peptic ulcer, and that is the old chronic ulcer in which such great changes have occurred at the site of the ulcer that the tissues have apparently lost their power of repair. Not infrequently in these cases we must dissect out the ulcer and either graft skin or cover the area with a flap by some plastic operation.

I would like now to ask you to keep in mind this picture of varicose ulcer as I have drawn it and apply it to the study of peptic ulcers. I think that very much the same thing happens in the ulcer in the interior of the stomach and duodenum that happens in the ulcer on the leg. If we can place a peptic ulcer under conditions in which we eliminate, as we can do in a varicose ulcer, the essential causes which produce and maintain the ulcer, we can in the vast majority of cases succeed in producing healing on the interior of the stomach and duodenum just as we can on the skin. In order to do this it is clear that we must place the patient at rest in bed, and we must place the stomach and duodenum at rest as much as possible. There is no doubt in my mind that rest in bed is desirable, certainly for three or four weeks. Local rest of the stomach and duodenum are obtained by removing food traumas and by the blandest possible diet. This, of course, is the practical method which we employ in clinical work.

We can demonstrate absolutely the value of rest in healing these peptic ulcers by the results which can be obtained from jejunostomy. If, for instance, under local anesthesia we pick up the first part of the jejunum

and introduce a small rubber tube into the jejunum, doing the operation with good technic so as to prevent any leakage and resulting peritonitis, and maintain this tube in the jejunum for a number of weeks, or even months, and put nothing of any kind in the stomach but feed the patient entirely through this jejunostomy tube, we in this way, of course, place the stomach and duodenum at absolute rest, and we can cure almost any of the peptic ulcers in the stomach or duodenum in this manner. That has been demonstrated now in a number of cases. I think we should keep this in mind as a definite illustration of the importance of rest in the healing of peptic ulcers.

In the third place, and very essential, is the neutralizing of the acid of the gastric juice so as to prevent the irritating digestive effects of the gastric juice on the raw ulcer surface. In the fourth place, of course, we must place the patient, handicapped as he is by being in bed, under the best possible hygienic conditions as far as food, fresh air and nursing are concerned to improve his general condition. In the large majority of peptic ulcers, rest of the patient in bed, rest of the stomach and duodenum neutralizing the gastric juice and improving the general condition of the patient will result in the course of some weeks, or possibly several months, in a complete healing of the ulcer. There are, however, definite exceptions to this rule. I think there is no doubt that old callous ulcers of the stomach and duodenum are often refractory, just as old callous ulcers of the leg are, to this rest treatment, and when the ulcer is situated so as to impair seriously functions of the stomach and duodenum, as at or near the pylorus, producing obstruction and deformity, complete wound healing cannot as a rule be obtained by medical management alone.

By the rather rough outline which I have drawn I want to present to you this conception that both the ulcer of the leg and the ulcer of the stomach and duodenum are the result of a number of causative factors; that when we recognize these factors we are in a position to apply this knowledge in a practical way in the cure of the disease; and that the cure depends on recognition of the principle that if we eliminate altogether, or a large part of, the causative factors, we can as a rule place the patient and the local lesion in a condition in which healing can go on to completion, and we can cure the disease. Although we can cure the great majority of peptic ulcers by a scheme of medical management on the principles which I have outlined, there remains a considerable number of cases, just as in ulcers of the leg, in which

we must resort to something more than medical management, namely, to surgical treatment.

We can cure a varicose ulcer of the leg by proper treatment. We can cure a peptic ulcer by proper treatment. We want to remember, however, that the ulcer in either case may recur, that it may recur at the original site, or a new ulcer may develop, and that this is apt to happen unless we take pains to eliminate to some degree at least the causes which produced the ulcer in the first instance.

In the case of the varicose ulcer the important factor of interference with return circulation can be remedied often by wearing a proper bandage or by a surgical operation removing a segment of the veins and breaking the long column of blood. In the case of the peptic ulcer, if we are to prevent recurrence, which is unfortunately common, we must by proper attention to diet and the general condition of the patient eliminate the acidity and food traumas, the nervous tension and the bad general conditions which were responsible for the ulcer in the first instance. The person who has been cured of a peptic ulcer must know that the price of a permanent cure is eternal vigilance, and this is true whether the cure has resulted from medical management or surgical operation.

Now let us turn to the surgical treatment of peptic ulcer. Surgical treatment includes operations for perforation, for pyloric obstruction, for hour-glass stomach, and operations for the actual removal and the resection of the ulcer. It includes also gastro-enterostomy and jejunostomy. There can be no question, of course, about the necessity and great value of the surgical treatment for perforation and for cicatricial and unyielding pyloric obstruction and for hour-glass stomach in which the deformity produces symptoms. All internists and surgeons agree that these conditions demand surgical treatment.

What can surgery do to cure chronic uncomplicated peptic ulcer of the duodenum and stomach?

1. The ulcer can be excised by one of several methods, and the patient cured by an operation which carries a certain amount of risk which varies enormously with the skill and experience of the operating surgeon.

2. Ninety per cent. of ulcers of the duodenum and 50% or more of ulcers of the stomach can be cured by a gastro-enterostomy, which again carries a certain amount of risk, probably less than 2%, in skilled

hands, with an associated risk of developing a jejunal ulcer in 3% or more of the cases.

How does a gastro-enterostomy cure an ulcer in the stomach and duodenum? This has been answered in several ways. Patterson believes that the important factor in the cure is the neutralizing of the acid gastric juice by the alkaline bile and pancreatic juice which results from their pouring into the stomach through the new opening. Admitting that there is probably some truth in this theory, I believe that the value of a gastro-enterostomy is in the safety valve action of the new opening. Let us apply this conception to a gastro-enterostomy for a duodenal ulcer in which the prospects of cure are, I believe, 90%. I visualize the result in this way: As soon as the gastro-enterostomy has been performed, a spasm of the pylorus occurs which prevents the gastric contents from passing into the duodenum, and as a result the gastric juice and food take the course of least resistance and pass out through the new opening. The duodenal ulcer is thus put at rest, is protected from the irritating actions of the gastric contents, and wound healing proceeds rapidly and the ulcer heals. As soon as the ulcer heals, or possibly even when it begins to heal and becomes covered with healthy granulations, the pyloric spasm lets up in whole or in part, and the gastric contents begin to take the normal course through the pylorus. In my mind one of the reasons for the marked relief which follows gastro-enterostomy is probably the relief from intragastric tension which the gastro-enterostomy affords. In the case of the cure of a gastric ulcer produced by a gastro-enterostomy I believe this relief from gastric tension, the freer emptying of the stomach and the neutralizing of the gastric juice by the bile and pancreatic furnish the logical explanation.

I have already referred to the cure of peptic ulcer by the operation of jejunostomy. Here the explanation is definite. The ulcer whether in the stomach or duodenum is at once placed at rest by feeding the patient through the jejunal tube, and healing usually goes on rapidly. The operation is, however, in spite of its efficiency, not a practical method of treatment and should be reserved as a preliminary procedure in seriously handicapped patients. I was in one case able to save a man's life by a jejunostomy, who had at the time of the operation only 17% hemoglobin.

What can be said of the operations for excising peptic ulcers? This can be done either by an oval or wedge-shaped excision, when the

conditions permit, or by transverse resection of the stomach, or by what is now being tried rather extensively—a resection of the stomach and duodenum by the Billroth 2 and the Billroth 1 operation. The excision of the ulcer seems the ideal treatment. The risk, however, is considerable. It is the operation of choice where it can be done without great risk and without resulting deformity. A new chapter is being written at this time in stomach surgery by the men who are doing the extensive resections of the duodenum and stomach, which are termed the first and second Billroth methods. These operations have proved, in the hands of a few expert surgeons, surprisingly successful. Moynihan, Haberer, and Clairmont, Eiselsberg and Schmieden have reported series of 50 or more cases with a death rate of 1-2%. I have personally been much impressed with the Billroth excision for ulcer and am trying it out in a series of cases, especially in cases of callous ulcers in which the possibility of carcinoma must be considered.

The Billroth excision accomplishes definitely three things:

1. It removes the ulcer.

2. It removes the pylorus and the element of pylorospasm.

3. By removing a considerable amount of the secreting surface of the stomach it diminishes the free hydrochloric acid content of the gastric juice; and finally it removes with the ulcer a possible existing or a potential carcinoma.

Now that we have reviewed the essential principles of this subject, let us ask ourselves how we shall apply this knowledge in actual practice, let us say in a hundred ulcer cases? I believe that we can make this matter simpler and clearer if we answer the question: With our knowledge of this subject, how would you and I like to have our ulcer of the stomach or duodenum treated? After all this is the real test. If I had a peptic ulcer uncomplicated by any of the conditions which we all agree demand surgical treatment—perforation, pyloric obstruction from scar, etc.—I would want to have it treated by a scheme of sound medical management and would place myself in the hands of my colleagues, Sippy or one of his disciples, because I believe that he has worked out the best method so far devised. I believe that my chances of cure would be 80 to 90%, and that I could keep well if I took reasonable care of myself. I would recognize the fact that there was a certain definite risk of recurrence. How large is difficult to state in figures.

If in the history of my case I had had repeated hemorrhages and the evidence showed that the ulcer was in the duodenum, I would want to be operated on by one of my good surgical colleagues who had devoted special attention to this subject. If in the course of the disease marked pyloric obstruction occurred, I would want to have a gastro-enterostomy performed. If in spite of good management I was not completely cured and symptoms recurred on slight provocation, I would want to have a gastro-enterostomy performed. If in spite of good management of the ulcer the symptoms persisted, I would want to be handled as a carcinoma suspect and be given the benefit of an exploratory operation. If at the operation a callous ulcer was found, I would want the benefit of a second Billroth operation. If I had an operation for ulcer, either a gastro-enterostomy or a resection, I would want to be given medical ulcer management as a part of the after-care for the purpose of reducing to a minimum the chances of a jejunal ulcer.

If I attempt to put the question of the medical and the surgical treatment of ulcer into figures, I would do so about like this: Almost all ulcers in their early history should be handled medically. When they persist under good medical management, when they recur in spite of good medical management and the care which the patient can obtain in his or her peculiar station of life, when serious and repeated hemorrhages occur, when pyloric obstruction does not yield to good medical management, when there is a reasonable suspicion of malignancy, medical management should not be too long persisted in but should give way to exploration and surgical therapy as the safer plan and the plan which affords the better prospect of cure. Numerically I believe that the cases demanding surgical treatment would include about 10% of the ulcers of the chronic type.

To visualize this a little more clearly let us take 100 cases of peptic ulcer. Practically all of these patients should be given at first the benefit of sound medical management. Possibly 90% of these can be cured and kept well by medical management. Probably 10% after repeated trials of medical management will prove refractory and should then be given the benefit of exploratory operation and surgical therapy. I have no sympathy for the position taken by some surgeons that ulcer of the stomach and duodenum are conditions like gallstone disease that are to be relieved by surgical operations. Nor have I any sympathy with the position taken by some gastro-enterologists, that all ulcer cases must be handled medically and that surgical therapy should be postponed

as long as possible and should be regarded as a last resort. To my mind the great value of medical management has been clearly shown, especially by Dr. Sippy and his disciples. They have shown that peptic ulcer can be cured by medical management, and that the great majority can be so cured.

On the other hand, no more brilliant chapter has been written in the history of surgery than the chapter on gastric and duodenal ulcers. We owe to our surgical colleagues most of the knowledge that we have of gastric and duodenal ulcers; the knowledge which we have obtained by necropsies in vivo which we have made during the last twenty years. Twenty years ago we hardly knew that there was such a thing as a duodenal ulcer. The surgeons furnished us with the knowledge of its existence and its frequency. The surgeons made mistakes in the development of this subject. They performed too many gastroenterostomies. They placed too little value on medical management. But in spite of mistakes, great progress has been made, and today we can say with much confidence that when ulcers prove refractory to medical management, modern surgery offers much to the patients. The ideal situation is the joint handling of these cases by an internist and a surgeon who both realize the field of usefulness and the limitation of both the medical and surgical management, and who give to their patients the benefit of their combined judgment and the treatment demanded in each individual case.

DISCUSSION

B. W. SIPPY: From my point of view, Dr. Bevan has presented this subject in a sane manner. With a few modifications, most of them of minor importance, the statements that he has used might well express my views on the subject, so that what I shall have to say to you will be largely a repetition or amplification or presentation of the same views with a combination of words a little different than he used.

My program stated that the paper was on "The relative value of the medical and surgical treatment of ulcer and the indications for each." I like that title much better than "The surgical versus medical treatment of gastric and duodenal ulcer." Medical versus surgical implies an antagonism, a conflict. The other title I like better.

Now, there are a number of factors entering into the relative value of these two procedures. I should say that they might be collected into three great factors that stand out: The first factor, is the conditions that attend the ulcer. The second great factor, and it is a most important one, has to do with the character or type of surgical management to which the patient is subjected, the skill of the surgeon who is to do the operation standing foremost. The third factor that has to be considered is the type of medical management that is to be instituted and the efficiency of it.

The particular type of medical management in common use the world over is the Leube and its various modifications, which consist in putting the patient to rest, giving good nourishing food. In many instances the ulcer heals, and, particularly if the treatment is instituted early, the treatment will result in a cure in many cases. My conception of peptic ulcer is that many of the ulcers that develop are symptomless and heal without trouble. Most of the ulcers that develop in the stomach we do not see and the surgeon does not see them, but they heal and leave a scar. That is why the pathologist finds ulcer more frequently in the stomach than in the duodenum, and we as clinicians find them in the duodenum more frequently than in the stomach. We must analyze carefully these important factors before we are ready to talk about the relative value of these two procedures.

Relative to the first factor, the conditions and complications that attend ulcer, they have a most important influence. Necessarily to evaluate them properly we must have an accurate diagnosis. An accurate diagnosis must show first, whether an ulcer is present; second, what complications if any exist, and third, what is the probable location, the extent and whether it is movable or not; is it on the stomach side of the pylorus or on the duodenal side of the pylorus; how deep is the ulcer, how broad; how long has it existed; if recurrences have occurred, how frequently? By main complications we mean is a cancer present or is pyloric obstruction present; if so, is it due to pylorospasm, inflammatory swelling, local peritonitis or is it due to a cicatricial narrowing? Is excessive secretion present; are gastric adhesions present; are perigastric abscesses present? Is an hour-glass stomach which interferes with the motility of the stomach present, or is hemorrhage depleting the patient? If one knows what to look for and how to go at it, it does not take long to determine about these things. When we know these things we are able to say whether the patient should be treated medically or surgically. The question does not become a general one of whether to treat medically or surgically, but the question is whether this particular case with all these circumstances present is one to be treated medically or surgically.

There are certain definite indications for surgical treatment. Dr. Bevan has named some of them. These are absolute indications. If there is a reasonable reason for suspecting that cancer is developing an operation should be performed at once. Perigastric abscess is a surgical lesion. Many patients with hour-glass stomach may be well treated surgically. I have mentioned perforation. Acute hemorrhage is seldom treated by the surgeon. Chronic hemorrhages are amenable to medical management when peptic ulcer is treated. One of the easiest things we have to deal with is persistent oozing. When these complications that may attend ulcer and may be mechanically removed are set aside as clearly surgical, what can the surgeon do to promote the healing of the ulcer? Let me say that in pyloric obstruction through our experience we have learned that 85% are relieved by careful medical management. The introduction of free hydrochloric acid takes away the most important irritant. The symptoms let up, the acute inflammatory swelling lets up and the motor meal will pass in the normal time in two or three weeks. Fifteen per cent of the patients will not improve. These cases are surgical in the presence of a good surgeon and no contraindications.

When the cases which are on a mechanical basis have been set aside, what can the surgeon do? There are certain instances in which the ulcer is so located that it may be excised, in which it may be reduced in size by the cautery; a resection of the stomach may be performed. These operations, such as excision,

resection of the stomach, etc., are not to be made unless they are made by an expert. The mortality in the hands of an expert is not high, but when made by those who are trying to imitate the experts the mortality may vary from 1 to 100%, depending on the skill of the operator.

Is it necessary to perform these operations of excision? You know how Moynihan feels about it. He says it is not right to excise an ulcer or cauterize it and perform a gastro-enterostomy. He says ulcers of the stomach can be treated by gastrectomy. He has a mortality of 4.7% and he can get away with it. Imagine what the mortality will be if the average surgeon is to do the operation. An ulcer may be so old or so large or both that the condition cannot be cured without excision of the ulcer. Let it be done by the expert. This involves the second factor in the management of ulcer—the character or type of surgical management and the skill of the operator. If we had experts only a patient with an ulcer would be reasonably safe in their hands, but experts are not going to operate on the vast majority of patients with ulcers. If surgical treatment is the only treatment that can be employed with fairness, then operators all over the country will try to imitate the experts.

What does a gastro-enterostomy accomplish? My conception is not quite the same as Dr. Bevan's. With a gastro-enterostomy the stomach empties itself in normal time. The 24-hour retention is reduced to from 9 to 12. The same is true of ulcer on the lesser posterior curvature without perforation unless it produces hemorrhage or is located on the stomach side, producing obstruction. The duration of contact of the irritant is not as long as in duodenal ulcer when it is obstructing. This duration of the contact of the irritant—we will not say what it is, theoretically it can be a number of things—varies considerably. This irritant is allowed to go out in normal time after a gastro-enterostomy. That places ulcer of the duodenum in the same position for healing with the action of the irritant as a posterior wall ulcer or a lesser curvature ulcer. If the common conception of the duration of contact of this gastric juice, as Dr. Bevan brought out, is removed in a few hours, the nutrition of the ulcer may be sufficient to go on and held even in the presence of a few hours of corrosive substance.

What does a gastro enterostomy do aside from relieving the obstruction? So far as anybody knows, nothing else can be done. Can this be accomplished by any other means? If the common conception of peptic ulcer is correct, namely, that the gastric juice produces the greatest hindrance to control, it follows that the healing of the ulcer will be accomplished by a means best adapted to relieve this peptic activity. It is done by the means we have been employing for the last seventeen years. We presume that the gastric juice has nothing to do with the healing. When the ulcer is well nourished, the gastric juice has nothing to do. It is only when there is a corrosive action that the gastric juice produces trouble. When that is well managed we believe the vast majority of ulcers will get well. Every one agrees that peptic ulcer, except when there are absolute surgical indications, should be treated medically. Let us have an active educational campaign to that effect all over the country.

A. A. STRAUSS: I was much interested in Dr. Bevan's statements regarding the pain produced by ulcer from intragastric tension. There is no doubt that in any viscus in which there is tension within the lumen there will be marked pain. However, I believe the greatest amount of pain is due to the peristaltic wave and increased contractions that pass over the chronically inflamed ulcer. This corresponds to the character of pain which the patient always complains of when the ulcer is located in the pyloric region of the stomach. Patients always

say that the pain lasts only for a minute or so and then reappears, which corresponds to the peristaltic wave in the pylorus. I have some doubt as to the amount of pain that is produced by the contact of the hydrochloric acid with the ulcer. I have operated on two patients with lesser curvature posterior wall ulcer under local anesthesia, in whom the anterior wall of the stomach was opened and a large posterior wall ulcer exposed. I made the following tests on these patients: I took about 30% hydrochloric acid and dropped it into the hollow of the nest-shaped ulcer; the patient stated that he had no pain. The same strength of hydrochloric acid was placed on the normal mucosa of the stomach, and he said he felt a burning sensation. We took sterile test-tubes which contained boiling water and put them in the callous part of the ulcer, and the patient did not experience a feeling of heat as he did on the normal mucosa. Both patients gave the same reaction to heat and hydrochloric acid. I think it is fair to assume or at least it is suggestive that the normal mucosa seems much more sensitive to acid and heat than does the calloused ulcer; this makes the amount of pain produced by hydrochloric acid in ulcer doubtful. The argument that alkalis relieve the pain is more easily explained on the basis that the alkalinization of the stomach contents relaxes the pyloric sphincter and relieves the intragastric tension and pylorospasm.

I also want to call attention to the fact that many of the patients with ulcer, who have had the greatest amount of pain have a normal or subnormal acidity. I mean by that they have a great deal of pain and show by fractional test meals that they have a subacidity.

I believe that the best surgical treatment for duodenal and gastric ulcer is excision of the ulcer with simple pyloroplasty. The mortality is no higher and probably lower than from any other surgical procedure and takes no more surgical skill than simple gastro-enterostomy and is much less of a surgical procedure; in fact, it can be spoken of as a minor operation as compared with gastro-enterostomy or partial gastrectomy. I also believe that by cutting away the sphincter muscle of the pylorus down to the mucosa, over somewhat less than one half of its circumference, and back on to the pyloric antrum for about 1 inch in the form of a pyramid with its base at the pyloric ring, more has been accomplished in giving the stomach a normal or quicker than normal emptying time than by any gastro-enterostomy, and it is a minor operation which takes about two minutes to perform as compared to the major operation of gastro-enterostomy. We have quite a large series of these cases and find them far more satisfactory than gastro-enterostomy. This pyloroplasty does away with the very point that Dr. Bevan brought out, that when you do a gastro-enterostomy you do away with the pylorospasm. So when you excise the ulcer and do a pyloroplasty you have removed the lesion and have given the stomach a normal or quicker than normal emptying time, but in addition you also have left the stomach and duodenum in their normal anatomic and physiologic relationship, which is not true by the other types of operation, such as gastro-enterostomy or partial gastrectomy.

I have had quite a large series of simple ulcer excisions and partial gastrectomies with a very low mortality, but I cannot say that the patient with half a stomach feels as well as the patient with a whole stomach. As to the mortality, and in answer to Dr. Sippy, who stated that only expert surgeons should perform these operations: When you sum up the cases of gastric ulcer treated medically that are found to be malignant a year or so later, and the cases that perforate during or after medical treatment, and those that have fatal hemorrhages during or after medical treatment, and the posterior wall ulcers that

perforate and infiltrate the pancreas—summing up the mortality and these end results which occur during and following medical treatment as compared with good surgical treatment, which has a mortality ranging from 2 to 4%, I think the statistics will be in favor of surgery, especially if we analyze the ulcers which we treat medically for several years and which then become malignant.

I also want to state that a far larger number of surgeons are doing partial gastrectomies and ulcer excisions, of whom we never hear unless we go out through the country to inquire about them, who have a mortality of 2 to 3%. I think there are many, who are learning gastric surgery in our laboratories of surgical technic and who have perfected themselves, that are now learning to do good gastric surgery. I believe that they should be encouraged rather than discouraged, and if so, the standard of surgery in this particular line will show marked progress in a short while.

There are a large number of cases of posterior wall ulcer that perforate into the pancreas, and which many have treated by simple gastro-enterostomy. This, I believe, is unsatisfactory since the patient has the constant pain of a chronic infiltrated and inflamed pancreas. I have operated on 16 patients with this type of ulcer by partial gastrectomy, and I believe the simplest method of attack is by opening the anterior wall of the stomach, which will permit one to see the exact extent of the changes. Then by freeing the lesser curvature one can separate by blunt dissection the adherent posterior wall and the ulcer from the adherent pancreas. A partial gastrectomy should then be made, which I believe is the only type of operation which should be attempted for this type of ulcer.

As to the merits of medical and surgical treatment: I shall answer the question Dr. Bevan asked. If I had a duodenal ulcer, I would have it treated medically. If it did not heal the first time, I would take a second medical treatment; but the economic condition of the patient should be considered. You cannot treat medically for months and months a poor man who has to earn a living for a large family by hard physical labor. You can keep him confined to a hospital or resting in bed only for a certain length of time, while with a wealthy patient this point does not need consideration. On the other hand, I believe chronic gastric ulcers should not be treated medically, but surgically.

ARTHUR DEAN BEVAN: I have nothing to add except to say that medical men and surgeons are writing an interesting chapter on this subject. I am much encouraged to feel that those who are studying these questions from both sides are getting nearer together and that in consequence we are obtaining better results.

CHRISTIAN FENGER AS I KNEW HIM

L. L. McArthur

March 10, 1922

The profound impressions created by the advent into these medical circles of such a master mind as that of Christian Fenger can be fully appreciated only by one preparing himself for the practice of medicine and surgery during those epochal transition years between the older humoral or other theories of diseases and the present era of scientific medicine.

Until that period, there had developed in each succeeding generation and in varying countries some outstanding thinkers, who, condensing the wisdom of the sages and adapting it to their personal conceptions of disease, after years of intelligent observation had evolved their own theory and practice of medicine. They endeavored to impart these to their students, with varying success. Certain ones acquired an earnest band of ardent followers, who formed a so-called "school."

To one who had sat at the feet of, and imbibed his earliest impressions of medicine from, such acknowledged thinkers of this community as J. Adams Allen, Moses Gunn, Hosmer A. Johnson, and Nathan S. Davis, would come more sharply the consternation at the radical changes made necessary by the newer pathology, morbid anatomy, and bacterial proofs submitted by the newcomer. He, too, could note more acutely the trace of opposition attendant on the substitution of demonstrable facts for long held plausible theories and sense the tinge of resentment ever directed against an iconoclast. On the other hand, it was a veritable pleasure to watch those beloved masters, as the evidence grew, endeavor to adapt themselves to the new truths as soon as they were demonstrated. Only big broad minds could thus unlearn the teachings of a lifetime, only the love of truth for truth's sake change such set convictions.

Thus, Christian Fenger, coming to Chicago, exerted an influence on Western medicine and medical teachings most revolutionary in character and impressive in extent.

Who, then, was Christian Fenger? When the King of Denmark deigns to honor one of his countrymen by knighthood, the one so honored is required to submit an autobiography for the government records. From such an autobiography by Christian Fenger, Knight of Dannebrog, written with never a thought of its ever appearing in

print, in his prosaic methodical manner, we learn all that is known of his early life. Through the painstaking labors of Dr. Ludvig Hektoen and Dr. Coleman Buford, this autobiography has been translated and serves as an admirable preface to the two volumes of "The Collected Works of Christian Fenger," 1840-1902, assembled by them.

A scholarly summary of Fenger's activities as a pathologist by our pathologist, Dr. E. R. LeCount, so thoroughly covers the field, that I shall refer you to his address before the Chicago Pathological Society, 1903 (incorporated in their proceedings). Dr. LeCount said:

He was born in Jutland on a fine old estate, formerly a monastery, belonging to his father and called Bregringgaard. This is on the west coast of Denmark, near the small town (500 inhabitants) of Rinkjöbing, in an agricultural district, the nearest large place, Aarhus, being 60 miles away on the eastern coast. His preliminary education was obtained at Herlufshalin, 30 miles from Copenhagen, where he spent nine years in a boarding school. He did not particularly distinguish himself here, being hampered by poor sight and a weak knee; recrudescence of the joint trouble also interrupted his medical studies. At the age of 19 or 20 he entered the University at Copenhagen and spent seven and one-half years, obtaining his degree in 1867. During his internship of two years in the Frederik's Hospital he wrote his first articles, but his duties at the "Kommune Hospital," where he was prosector (resident pathologist) for three years, did not begin until 1871, after his service in the Franco-Prussian war as a surgeon.

It would be edifying indeed to know the primary factors influencing his early training, the dominant qualities of the men who taught him and whom he earnestly sought to emulate, his first great ambitions and how they arose. Among his ancestry and in his family a tradition exists that one great physician appears in each generation. A Christian Fenger born in 1773 held many honored positions as a surgeon, and was "ausserordentlicher" professor at the "Akademie" in Copenhagen. Two years before his death in 1845, his nephew, Carl Emil Fenger, was appointed to the newly created lectureship in pathologic anatomy and general pathology at the university. This Emil Fenger was at the zenith of his activity in medicine when the man we learned to respect so highly was an undergraduate. Although the writings of Emil Fenger in medicine were mainly on mortality statistics, he is credited with emancipating medical education in Denmark from the dominance of humoral pathology. This service was largely performed through a polemic with his colleague Buntzen, and originated with an attack by Buntzen on the development of experimental physiology and pathologic anatomy instigated by the growing skepticism for the time-honored empirical therapy.

Buntzen criticized research for its failure to provide definite guiding precepts to therapy and for the large personal element entering into its results. Fenger's reply, entitled "Contributions to an Elucidation of the Present Movement in Therapy" (translated), ran through seven numbers of the hospital journal. Its minutiæ cannot be examined here, but it will interest you to learn that his clear conception of the entire problem, his defense of investigation, and distinctions between 'Haltbar' and 'unhaltbar,' not only cleared the atmosphere of doubt and uncertainty for the younger men in the profession, but

denoted a decisive and commanding mentality. Although this episode of Danish medical history sheds faint light on the conditions prevailing when Fenger studied medicine, it is pregnant with revelations of the personality of Emil Fenger, his uncle.

During the latter part of our Fenger's undergraduate work in medicine, there came to the University a distinguished physiologist whose influence we have good reason to believe was responsible to a large degree for his conceptions of scientific work. Panum had previously occupied the chairs of physiology, general pathology and medical chemistry at Kiel for five years. He was not only a pupil of Claude Bernard, but had served as his assistant for a number of years before going to Kiel. His advent in Copenhagen was followed by the introduction of new scientific methods of studying and teaching physiology.

Two years before Fenger graduated, Hans Wilhelm Meyer began his special clinic of throat, nose, and ear diseases, and while an intern in the Frederik's Hospital Fenger devoted considerable time to attending this clinic. It was at this time (1868) that Meyer's epochal work on adenoids of the nasopharynx appeared in the *Hospitalstidende*. There is evidence that these three men—Emil Fenger, his uncle, Panum, the physiologist, and the clinician Meyer—were largely responsible for Fenger's scientific medical training.

In the medical faculty at this time Schmidt, a pupil of Kölliker and of His, was the anatomist; Reisz, who had studied with Virchow in 1861, held the chair of pathologic anatomy; the surgeons were Mathias Saxtorph, Stein, and Buntzen; Dahlerup and With taught internal medicine; Warncke pharmacology; Englested venereal diseases and dermatology, and Stadfeld obstetrics. Many of these teachers wrote textbooks; Engelsted's treatise on the clinical aspects of constitutional syphilis was translated into German. Buntzen founded the *Hospitalstidende*, and was for many years its chief editor; Panum, with Key of Stockholm, the *Nordiskt Medicinskt Arkiv*; and Emil Fenger the *Hospitals-Meddeleser*, which Petersen, the Danish medical historian, has pronounced a literary movement. It is obvious from the foregoing that Fenger's professional education was acquired under auspicious circumstances and in an atmosphere replete with personal impressions of men responsible for many important advances in medicine. When Panum came, as before stated, during Fenger's student days, it was to take the place of Eschricht, who had studied with Majendie and been a personal friend of Johannes Müller and von Baer. We can readily believe that the principles of scientific work so thoroughly understood by Fenger were, at least in part, transmitted to him, through Panum, from Claude Bernard.

My early medical career having brought me in such direct contact with him whose memory we are here to honor, you will, I trust, pardon me if the reminiscences partake of a rather personal character. Coincident with my entrance to Rush Medical College (1877) was the advent of Dr. Fenger to Chicago, where he was induced by his friend, Dr. S. D. Jacobsen, to locate permanently. As a student at, and later as intern on the staff of, Cook County Hospital, I learned to know Dr. Jacobsen intimately as a sterling, scholarly, learned medical man—and his was clearly the influence on Fenger determining his future career as a Chicagoan. Dr. Jacobsen at that time had charge of the eye and ear

department at the Cook County Hospital, and parenthetically, all wise candidates for his vote were at least familiar with the anatomy of Jacobsen's nerve, first described by his uncle. An enlightening remark by Dr. Fenger, in his autobiography, to those familiar with the existing conditions is the following: "In 1878, I secured 'by *means of borrowed money*' a position on the staff of Cook County Hospital." At that period, the most corrupt group of county commissioners Chicago has ever had were in control. One thousand dollars was the price for a place on the staff of an institution for the care of the poor of Cook County! An ambitious medical man, with no other reward than to see, study, and heal disease, was compelled to buy his appointment during their regime! I doubt not Dr. Jacobsen was his financial aid.

These first two years of Fenger's service as pathologist at Cook County Hospital exerted a profound effect on the writer, then a student at Rush. As a newcomer and with few friends, Dr. Fenger was given for his clinic the inconvenient hour from one to two—an hour never before assigned to an attending man for a clinic. Twelve to two, in all preceding years, was set aside for luncheon, rest, and recreation. Following custom, the students failed at first to attend in any large numbers. Thus it happened that Dr. J. B. Murphy and myself, fascinated by his wonderful technic in making a postmortem examination, thrilled by the revelations each necropsy offered, and rewarded by his efforts to convey to us the information that should have gone to the entire class, were constant attendants during these first months, one taking down the findings, the other sewing up the cadaver. Undoubtedly, this experience remained ever after a potent factor in J. B. Murphy's future development, as was later true of so many others.

Christian Fenger, although wonderfully well read and a *great* linguist, labored under a peculiarly halting speech that to those hearing him for the first time proved difficult to follow—hence the scant attendance of his classes. One wag remarked "Fenger could stammer in seven languages." The wealth of knowledge in this new world of pathologic and morbid anatomy repaid a thousand-fold those ignoring his poor delivery.

So great was Dr. Fenger's pleasure in conveying his knowledge to those manifesting genuine interest that he frequently forgot engagements, patients, even his meals, while trying to make clear some problem in pathology. Indeed, some of the interns at the County Hospital, in their eagerness to obtain his opinion as to the nature of some obscure

cases would ask him to see the patients. Willing to oblige, Dr. Fenger would see the patient and make the pathologic diagnosis. His diagnosis was frequently at variance with that made by the attending surgeon to whom the case had been assigned. This once resulted in a curt communication to Fenger. Dr. J. B. Herrick will recall the effort made by an intern on a later occasion to induce Fenger to state how a certain fracture of the thigh could be handled. He replied, evasively, "Many roads lead to Rome." Still persisting in asking him how he would have treated it, Fenger, not to be betrayed again, said, "Listen! you let the attending surgeon in charge of that case treat it the way he wants to."

Fenger, early in his career, served with a battery in the Danish-Prussian War, 1864 (?). His experimental work on bullet wounds and their endoscopy following this experience was so much appreciated that a special grant was made by the Minister of War in order to allow him to continue his experiments in the Franco-Prussian War. Naturally, then, when Pasteur had demonstrated the relation which certain bacteria bore to disease in man, and Lister had demonstrated the possibility of killing or keeping them out of wounds, Fenger quickly saw and accepted the importance of surgical antisepsis and asepsis. In this he was a pioneer. The introduction of Listerian methods in the County Hospital through the influence of Christian Fenger, caused me physical pain, for I was the Junior to whom was delegated the dressing of every open wound or sore. Thus, in the Hospital, all of the leg ulcers, inflamed, ingrowing toe nails, felons et id genus omme, must be dressed under a spray of 5% phenol, washed with 2.5% phenol covered with eight layers of gauze, one layer of mackintosh, and a ninth layer of gauze outside—a useless layer. This meant dressings from 8 a. m. to 6 p. m. daily—and no trained nurses! But soon there began to be healings "per primam," shown at first with pride to the staff and interns and later as something to be expected; finally, if the desired result was not obtained, it was a reproach to someone.

After the first two years as pathologist at Cook County Hospital, he had so thoroughly impressed the staff with his familiarity with surgical problems that the members of the surgical staff left him in charge of their services during vacations. With these opportunities for surgical demonstrations, appointment as attending surgeon soon followed, and for fourteen years he was actively engaged with every kind of surgical problem. During all these years, he constantly accumu-

lated specimens of every type of surgical pathology. Whenever a subject of special interest came up in the societies he would discuss it, submitting abundant specimens in proof of his arguments. These specimens were always at the service of his friends. He frequently helped fill baskets with specimens for his friend, Nicholas Senn, in Milwaukee.

To him, too, the younger surgeons turned hopefully as a sheet anchor in their pathologic difficulties. I recall vividly an acute malignant edema infection in a wound of the thigh severing the quadriceps tendon, which I had sutured 24 hours before. The patient, who had fallen down the hospital shaft, was a protege of the president of the hospital—hence my anxiety. At midnight on a stormy winter night 30 years ago, I rang his doorbell. The little square panel in his door opened. I told him my dilemma. "Wait," said he. He dressed quickly, drove with me to the hospital, saw the patient, and said, "The diagnosis is correct; the infection is now at the midthigh, in the morning it will be above the groin, at noon at the umbilicus, at night he will be dead; do not amputate—you have done everything possible—good night."

Christian Fenger, kindly by nature, never intentionally hurting another's feelings, was nevertheless so bluntly outspoken as to be brusque at times, and chilled friendships that otherwise would have been strong ones. Never politic, when asked for an opinion in a consultation he gave it, without consideration as to what had gone before or the former opinions offered; while the more polished but no more sincere consultant would have glossed over the differences, and accomplished the same good for the patient. The following personal experience illustrates this lack of tact. At a meeting of the Chicago Surgical Society, at which Dr. Fenger presided, I presented my first combined resection of liver and stomach for carcinoma, with patient, specimens and microscopic slides. Before calling for the closing of the discussion, Dr. Fenger arose and said: "I have examined the specimens and the microscopic slides. In these, I note it to be an adenocarcinoma. It is invading the liver tissue without showing a limiting membrane. It will recur within the year with exitus." And the patient was seated directly in front of him! Who knew more about cancer of the stomach than Christian Fenger? His prize essay on "Carcinoma of the Stomach," a classic, was one of the earliest and best descriptions ever written and is never omitted from the bibliography of this subject. To him the world is indebted for the discovery that much of the pain

associated with this ailment is due to the direct invasion of the nerve trunk supply itself by metastatic tumors, specimens of which he submitted with his thesis.

All great men have a hobby, and Fenger's was music. When he desired respite from work he would play on the piano. Accidentally, I learned of his love of music. Many years ago, in the old Exposition Building on the lake front, the opera "Aïda" was given by an all star cast. Campanini, Gerster, Emma Nevada and Scalchi took part. My seat was next to Fenger's. During the intermission, he told me of his service with the Khedive of Egypt who bankrupted the treasury of his country by his extravagances, one of the greatest of which was the ordering of that opera to be composed for him by Verdi for the celebration of the opening of the Suez canal and in honor of the coming of Napoleon III. Carte blanche was given Verdi to secure the best singers in the world. They came from Berlin, Paris, St. Petersburg, Vienna, and London at their own price! No expense was spared in staging the opera in Cairo, the only stipulation being that it should extol the grandeur of Egypt. As an officer in the service of the Khedive, he was provided with an excellent seat at the prémière. Years later in Chicago, the memories of those scenes were again recalled to him vividly and with an evident thrill. Turning to me, he said, "McArthur, I believe the singing and the orchestration equally good, but, oh, the magnificence of the mise en scène and the brilliant audience will never be duplicated!"

To one who served at one time as Fenger's house surgeon and later grew up in his environment, after the lapse of two score years the conviction is fixed that Fenger was a great and a learned surgeon. De mortuis nil nisi bonum will still permit an ardent admirer and a grateful student to remark: He was not an equally brilliant operator. His exact knowledge of surgical anatomy, his dead-house familiarity with every part of the human body seemed to influence the extent of his incisions. His thorough understanding of the existing pathologic process, his scientific urge to be thorough, would ofttimes prolong an anesthesia to a dangerous length. With his faults (and they were few), we loved him for himself and for what he taught us.

"So when a great man dies,
For years beyond our ken,
The light he leaves behind him lies
Upon the paths of men."

THE EDWIN SMITH PAPYRUS

AN EGYPTIAN MEDICAL TREATISE OF THE SEVENTEENTH CENTURY BEFORE CHRIST *

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CHICAGO

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In the middle of the twenty-eighth century before Christ the Pharaoh Neferirkere was one day inspecting a new building in course of construction under the superintendence of the chief architect Weshptah. The king and his court were all admiring the work and the Pharaoh was turning with words of praise to his faithful minister, when he suddenly noticed that Weshptah was unable to hear the words of royal favor. The king's exclamation alarmed the courtiers. The stricken minister was quickly carried to the court and the priests and the chief physicians were hurriedly summoned. "His majesty had brought for him a case of writing. . . . They said to his majesty that he was lost." Such are the words of the ancient inscription in which the incident is recorded. The king, smitten with sorrow, can only retire to his chamber in prayer and order sumptuous arrangements for the great man's interment.

The mortuary inscription of Weshptah which thus narrates his death incidentally furnishes us, therefore, the earliest historical reference to medical literature. Unhappily none of the books as old as those which the Pharaoh's physicians consulted on behalf of the dying royal architect has survived to our day. A thousand years after the incident above narrated—that is, at the dawn of the Egyptian Empire or later—the Egyptian physicians endeavored to give authority to the medical literature they used by representing it as having descended from the venerable Pharaohs of even earlier days than those of the dying architect of Neferirkere. The London Medical Papyrus, a worthless compilation of medical magic, informs us: "This book was found in the night, having fallen into the court of the temple in Chemmis (?) as secret knowledge of this goddess (Isis) by the hand of the lector of this temple. Lo! this land was in darkness and the moon shone on every side of this book. It was carried as a marvelous

* Read before a joint meeting of Society of Medical History and the Institute of Medicine of Chicago.

thing to the majesty of King Khufu (Cheops)." Similarly, a section of the Berlin Medical Papyrus claims to have been "found in ancient writings in a chest containing documents under the feet of Anubis at Letopolis in the time of the majesty of King Usephais, deceased; after his death it was brought to the majesty of King Sened, deceased, because of its excellence." If we were to accept these last two statements as historical we should be obliged to conclude that the medical writings of Egypt were some of them produced as far back as the First Dynasty, that is, in the thirty-third or thirty-fourth century before Christ. However this may be, there is no reason to doubt the existence of the medical rolls which were already numerous enough to fill a case in the days of the Pharaoh Neferirkere, in the twenty-eighth century before Christ.

Although we do not today possess any surviving rolls as old as those just mentioned, we have several fragments which belong to the Middle Kingdom (about 2160-1788 B.C.): scanty remains of a treatise on diseases of women, even a veterinary manual on diseases of cattle, and some very important still unpublished fragments, probably the oldest such material known, which will be edited later by Dr. Alan H. Gardiner. The most important medical works surviving from ancient Egypt are a group of four almost or entirely complete treatises of somewhat later date. Two of these are in America and two in Europe: Papyrus Ebers in Leipzig, and the Berlin Medical Papyrus in the National Museum at Berlin; the Hearst Papyrus in the collections of the University of California, and the new Edwin Smith Papyrus, the property of The New York Historical Society. Of these documents the Berlin Papyrus is the latest (about the thirteenth century B.C.), while Ebers, the Edwin Smith Papyrus, and Hearst, are much earlier. Papyrus Ebers dates from the beginnings of the Egyptian Empire in the early part of the sixteenth century B.C., while the script of the Edwin Smith Papyrus would indicate that it is probably slightly earlier, reaching back to 1600 or into the seventeenth century B.C. The New York Historical Society, therefore, is fortunate in possessing the oldest scientific book in America and the oldest nucleus of really scientific medical knowledge in the world. Among historical societies this is a unique distinction. It is gratifying to be able to add, also, the far more weighty fact that the Edwin Smith Papyrus contains incomparably the most important body of medical knowledge which has sur-

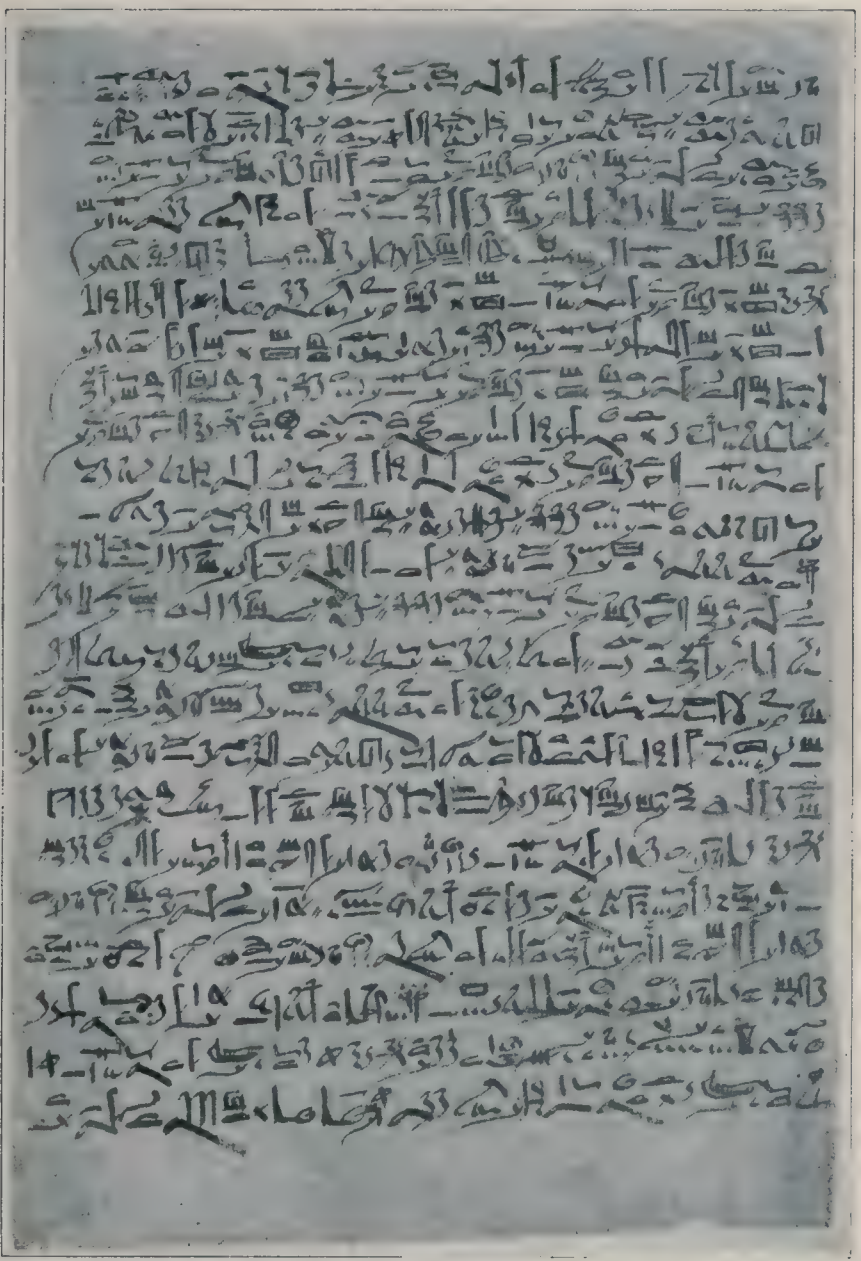


Fig. 1.—A page of the Edwin Smith Papyrus. The writing is the rapid cursive Egyptian hand, called hieratic, in which the original hieroglyphic pictures are abbreviated and rounded off until they have lost their picture form. The manuscript dates probably from the latter part of the 17th century B. C.

vived to us from ancient Egypt, or, for that matter, from the ancient Orient anywhere.

The history of the document is curiously interesting and throws a picturesque light on early oriental studies in America. Mr. Edwin Smith, after whom the document is named, and to whose daughter, Miss Leonora Smith, The New York Historical Society owes the gift of the papyrus, was the son of Mr. Sheldon Smith of Bridgeport, Conn., where he was born on April 27, 1822. The publication in April, 1922, of this preliminary account of the ancient medical document, which he discovered and brought to America, is therefore a very fitting commemoration of the centenary of his birth. His family later removed to Newark, N. J., and thence to New York City, where he was educated at New York University. By a curious coincidence Mr. Smith was born in the very year when Champollion accomplished his decipherment of Egyptian hieroglyphic. His youth thus fell in the years immediately following this epoch-making achievement. This may have been the reason why he early became deeply interested in the study of Egyptology and, after studying the subject in both London and Paris when the science was only a quarter of a century old, he went to Egypt about 1858. He lived in Luxor, ancient Egyptian Thebes, from that time until 1876. Then, after a brief visit in this country, he went to Naples, Italy, where he resided until his death, April 23, 1906. In the early part of 1862, during his stay at Thebes, he purchased the document which is the subject of this article.

I find among Mr. Smith's papers in handwriting so very like that of a note presumably written in the early sixties that it must have been made at about that date, a remarkable attempt at a complete translation of the document. When we remember that the knowledge of hieratic, that is, cursive Egyptian writing, possessed by scholars, and likewise the knowledge of the Egyptian language as a whole, available at so early a stage of Egyptian studies, was very limited, it is extraordinary how much of the document Mr. Smith has understood. He was fully aware of the character of the papyrus as a medical document and had gained a surprising amount of information regarding its content. It must be that during the course of his studies in London and Paris in the fifties of last century, he gained control of all that was known of Egyptian in those early days. We must, therefore, give him a high and honorable place in the history of

oriental studies in America.[1] I would like to mention, also, the fact that of the 8 fragments of the papyrus which, as we shall see, Mr. Smith rescued, he was able to place 3 with entire exactness and 2 more at least in their proper connection. His career in connection with oriental studies and with the discovery of this extraordinary document reminds one throughout of those gifted free lances in English oriental studies, like Goodwin in Egyptian and Rawlinson in cuneiform, who have done so much for the advancement of oriental science. And yet heretofore one would have looked in vain in the annals of oriental research for the name of Edwin Smith. It is eminently fitting, therefore, that henceforth this great monument of ancient oriental science should everywhere be known as the Edwin Smith Papyrus.

The Edwin Smith Papyrus is a roll having, as at present unrolled, a length of 184½ inch. (15 ft. 4½ inch., or 4.68 m.). As at least a column of writing has been lost at the beginning, its original length was demonstrably not less than 196 inch. (16 ft. 4 inch., or 4.97 m.). The papyrus makers of ancient Egypt furnished commercial rolls of conventional length, usually made up by pasting together 20 sheets some 16 inch. (40 cm.) wide, making a total length of the commercial roll about 320 inch. (26 ft. 8 inch.). If our papyrus was of the usual original commercial length,[2] we have then lost a little over 135 inch., or some 13½ columns. It is written on both sides, 17 columns (377 lines) on the front and 5 columns (92 lines) on the back. At present, therefore, there are preserved on both front and back 22 columns of writing, making a total of 469 lines, or, with the fragments and the additional column demonstrably lost, the document contained at least nearly 500 lines.

The arrangement in columns, made up of horizontal lines, it may be worth while to note, is the origin of the modern printed page. An examination of the two reconstructed rolls in Figure 4 will make this clear. The exposed portion of roll AB is covered with 50 vertical lines of writing numbered from right to left. This was the earlier Egyptian arrangement of a papyrus manuscript. It will be observed that it required no division or interruption in the text. After 2000 B.C.,

[1] See further information regarding Mr. Edwin Smith and his ability to read Egyptian, in the delightful account of the earlier Americans interested in Egyptology, by Dr. Caroline Ransom Williams (Mrs. Grant Williams) in the Bulletin of the New York Historical Society (April, 1920).

[2] Although the full length commercial rolls known to us are somewhat later than the Edwin Smith Papyrus, it is nevertheless highly probable that they were already current in the earlier time.

however, the Egyptian scribes began to write more commonly in horizontal lines, each line necessarily of limited length, so that the writing was divided into columns, as illustrated in the roll CD. In later times, after the rise of the great Alexandrian library, the cumbersomeness of the roll form of book led to cutting up the roll between these columns into pieces each having one column, and then fastening these pieces together at the edges in piles, thus producing the first cut book pages, of which the columns on the Egyptian rolls were the lineal ancestors.

The Edwin Smith Papyrus was a stately book. The papyrus is 13 inch. high and the columns themselves are between 11 and 12 inch. in height, reaching a maximum of 12 inch. in width, though some are as narrow as 7 inch. It was, therefore, from the Egyptian point of view, of full folio size, a form in which it is paralleled only by the great Papyrus Ebers, all the other medical papyri being a half sheet (about 6 inch.) or less in height. The writing gives us the rapid or cursive form of the originally hieroglyphic signs—a form known since Greek times as hieratic. It is done in a beautiful and regular hand, evidently the work of a skilled scribe, who was, however, unfamiliar with scientific literature. He has a very unhappy time with some unfamiliar words. For example, when he is compelled to draw the human jaw as a graphic "determinative," he makes a lamentable job of it. But he was evidently very much more than a mere bureau scribe, laboring for the production of merely commercial and other similar records. He made not infrequent mistakes, many of which he has corrected. The corrections are easily discernible because, like all Egyptian scribes, he has written the important introductory words of all his paragraphs and the subsections in red ink, the "rubrics" which passed into later European manuscripts and thus to us. When called on to make a correction, therefore, he did it with red ink over the black writing or with black ink over the red. In one place (column XI) he has omitted an entire phrase, which he has then inserted in the margin at the top of the page, calling attention to its omission by inserting a red cross at the proper place in the text. In some such manuscripts the cross is also appended to the omitted words in the margin, which are to be inserted in the text—thus showing us again where we got our asterisk. This does not happen to be the case in the Smith Papyrus. The entire front of the document is the work of one hand. It is possible, though not probable, that the first

3½ of the 5 columns on the back are likewise the work of the same hand, but the concluding section (columns XXI and XXII) are by a totally different and a later hand.

In taking up the content of the new papyrus we cannot avoid referring to the present limited state of our ability to deal with such a document and determine its content. Let the average man of today sit down to read a technical description of an automobile engine. He will undoubtedly find himself confronted in every line by at least one word of which he does not know the meaning—and this in twentieth century English! I recently sat at a dinner table where not a person present knew the meaning of the word "gasket." If such is our predicament when dealing with a highly specialized word in our own contemporary mother tongue, how much greater must be the difficulty when we are confronted by a body of specialized words. employed by the medical men of 3,500 years ago, writing a language which has now been dead for centuries. Our difficulty is increased by the fact that no one has ever yet carefully studied the medical documents of Egypt together as a group, or built up a carefully grounded glossary of the medical terms which they contain. So-called translations of the Papyrus Ebers have been made, with misunderstandings on every page which make them ludicrous, and much popular writing based on such translations has professed to give us some account of Egyptian medicine. Such a discussion is of course not only without value, but very misleading. On the other hand, Professor Wreszinski of Koenigsberg before the war had begun a series of preliminary publications of the available ancient treatises, together with concordances, and these initial studies are of the greatest value. Unhappily they have been suspended by the war. Useful studies of particular points or passages have been made by Schaefer, Erman, Maspero and others, and from the practical physician's point of view also by von Oefele. But a thoroughgoing study of the whole subject, based on all the surviving treatises, still remains to be made. We should have exhaustive studies especially of all pathologic, physiologic, anatomic, mineralogic and botanical terms appearing in these documents. Even when this has been done, there will be many words in these ancient treatises which we do not understand and many phrases which we cannot render. There are many such in the Edwin Smith Papyrus which I do not yet comprehend,[3] and that will undoubtedly be the case

[3] It is needless to say that the present writer possesses no more than the average layman's knowledge of anatomy.

when the final manuscript for the publication in extenso is ready. Another difficulty lies in the complete lack of any comparative study of these ancient medical books, or the symptoms and diseases which they describe, on the one hand, and on the other the surviving evidences of disease in the ancient bodies excavated by the thousands in the Egyptian cemeteries and studied with such success by Dr. G. Elliot Smith and others. I have inserted in this preliminary report on the new papyrus a few examples of these ancient bodies, to illustrate this side of the unexplored field. In reading the following account of the content of this new medical papyrus, then, the reader should bear in mind these fundamental difficulties which hamper our understanding of a treatise so specialized and so ancient. It may be remarked also that the treatise itself throws most interesting light on the meanings of some of the terms it employs, and persistent study discloses such unexpected revelations as the bit of fascinating ancient anatomic description—the oldest such description known—of the articulation of the human mandible with the temporal bone, as we find it in this venerable medical book.

The Edwin Smith Papyrus obviously falls into 3 different parts, drawn from 3 different sources.

1. The seventeen columns of the front.

2. The "Incantation of Expelling the Wind of the Year of Pest" (three and one-half columns of the back).

3. The "Incantation of Transforming an Old Man into a Youth of Twenty" (part of the last two columns of the back, XXI and XXII).

The second and third, mysteriously attractive as they may seem to be, are brief magical treatises. The second is made up solely of magic incantations, interesting as already containing the widely prevalent notion which has persisted even into our own day, that malignant plagues are carried by pestilential winds. It is possibly by the same hand as the front, the slight differences being caused by the difference in the direction of the fibers of the papyrus (horizontal on the front, vertical on the back). The last section was copied from some old source in a hand totally different from the other two treatises, as we have noted, by a later scribe who could not resist its attractions.

It is the seventeen columns of the front which make the Edwin Smith Papyrus unique. They contain part of an extraordinary ancient

book of surgery and external medicine which began its discussions with the top of the human head and proceeded in orderly progression downward to the lower members, presumably concluding with the feet. Though the divisions are not indicated by the ancient scribe, this treatise on the front falls into the following sections, represented by 48 cases:

1. Head (Calvaria) (Cases 1-10).
2. Nose (Cases 11-17).
3. Mandible, ear and lips (Cases 18-27).
4. Throat and neck (cervical vertebrae) (Cases 28-33).
5. Collar bone and shoulders (clavicle and scapula) (Cases 34-38).
6. Thorax and mammae (Cases 39-47).
7. Spine (Case 48, incomplete).

Unhappily the scribe who copied the original treatise suddenly stopped at the bottom of column XVII in the middle of a line and in the middle of a sentence, leaving blank at the end of the roll an entire sheet (16 inch.) of papyrus and cutting off the original treatise in the midst of the first case devoted to the spine. Stopping thus he has left us without any of the treatment of the human body below the thorax except the beginning of one case on the spine. When he, or possibly another copyist, resumed his work he turned the roll over and began to copy on the back the worthless incantations of the second part already mentioned. We should be grateful, however, for what the ancient scribe has done for us, for these 17 columns contain the most carefully made and most systematically arranged observations on the human body and its ailments which have thus far survived from an age so remote.

Each of the 48 cases is methodically arranged thus:

(a) Title, always beginning: "Instructions for . . ." (name of ailment).

(b) Examination, always beginning: "If you examine a man having . . ." (symptoms follow).

(c) Diagnosis, always beginning: "You should say concerning him: 'A sufferer with . . .'" (name of trouble follows).

(d) Verdict,[4] always one of three:

1. "An ailment I will treat." (favorable)
2. "An ailment I will contend with." (doubtful)
3. "An ailment I will not treat."[5] (unfavorable)

(e) Treatment.

(f) Explanatory glosses (seventy in all).

The first group (10 cases, 1-10) deals with wounds in the head, of which the first 7 are knife or sword wounds penetrating to the bone.[6] They vary in character according as the skull itself escapes injury or suffers contusion, a gash, a fracture, etc. In all these cases the surgeon is instructed in the examination: "You should probe the wound." If he finds only a contusion of the skull or no injury at all, the vedict is favorable; a gash in the skull, doubtful; a fracture in the skull (several kinds), unfavorable. Case 7, which occupies over 2 columns and is the longest case in the treatise, describes 3 different conditions of the injury to the skull under the knife wound, gives two verdicts (one doubtful, one unfavorable), and in the third condition says to the surgeon: "You should have made for him a wooden brace padded with linen, (and have) the head fastened to it . . . His treatment should be sitting, placed between two supports of brick, until you know whether he is making any progress." These contrivances are evidently devices familiar enough to the Egyptian practitioner to need no further description. The first might be variously explained but the second, built of sun-dried brick like the beds of the poor, is obviously intended to prevent the sufferer from lying down and disturbing a badly injured skull. It may be mentioned also that the examination in this case notes a feeble pulse and fever as among the symptoms. That the Egyptian surgeons had plenty of such cases to deal with is interestingly illustrated by the gashed skulls shown in the illustrations. The healed sword-cut illustrates the surgeon's ability to deal successfully with such injuries.

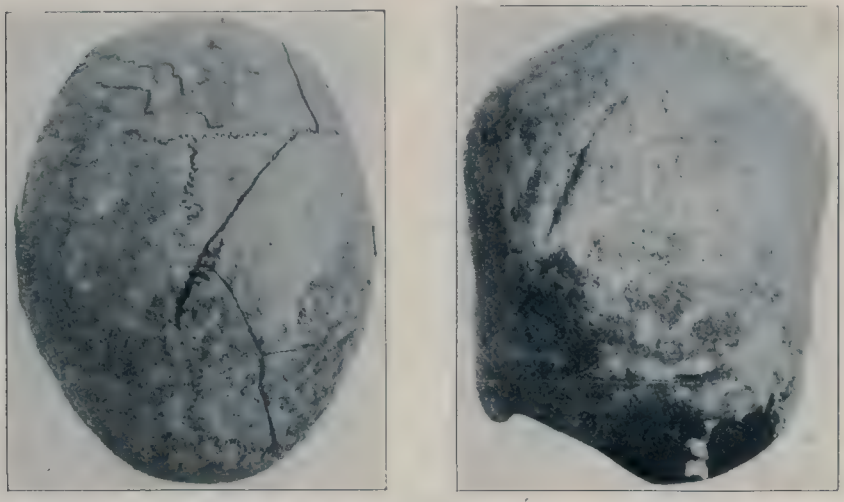
Case 8 deals with a "fracture of the skull under the skin." When examination has demonstrated the presence of the fracture, the surgeon is unconditionally charged to operate, to open at the point of contusion,

[4] Some such term (not drawn from the original) seems preferable to our modern "prognosis," which does not exactly correspond.

[5] Grammatically, this phrase is not clear in the original; but the character of the cases to which it is appended, and the wording of the phrase, make it clear that it characterizes a case as probably beyond the physician's power to treat successfully. For example, see case 33, a crushed cervical vertebra, and compare the case of the architect Weshptah, which the physicians pronounced hopeless.

[6] These wounds might also be due to the long-bladed Egyptian war axe of the Middle Kingdom.

and "to elevate the depression outward." It may be for the modern surgeon to decide whether this could be done without trephining; if trephining is involved, as would seem probable, we have here the earliest reference in literature to this famous operation. Although an operation known to have been practiced by peoples in a primitive state of culture, trephining has not yet been unmistakably identified on surviving ancient Egyptian skulls. In any case, the proposed operation was a desperate measure. The verdict was unfavorable, recovery doubtful and the patient was to be treated sitting up, as in Case 7.



Figs. 2 and 3.—Sword cuts in Egyptian skulls of a century or two before the Christian era. In Fig. 5 (left) the cut and the resulting fracture caused death; in Fig. 6 (right) the art of the surgeon healed the wound and the man survived. (From G. Elliott Smith and F. Wood Jones.) The Archaeological Survey of Nubia. (Report for 1907-1908.) Vol. II. *The Human Remains*, pl. XLI, Fig. 3, and pl. XLIII, Fig. 2.)

In the last two cases of this group (9 and 10) the treatise proceeds to the front of the skull: a knife wound in the forehead with fracture and a wound through an eyebrow. The cut in the forehead is to receive a plaster made of "physicians' skin"—a kind of linen bandage prepared by the embalmer; the cut in the eyebrow is to be carefully held together by a special "double bandage" so as to "cause the two lips of the knife wound to join one to the other."

A second group of 7 cases (11-17) deals with the nose and connected trouble: an uncertain affection in the "column (upper part) of

the nose," the same in the "inaccessible region of the nose," "fracture in the nose," a "wound in the nose" which penetrates to its interior, and so on. In treating the trouble in "the inaccessible region of the nose" the secretions are to be cleared away by using "two swabs of linen" and thereupon "two rolls of linen dipped in ointment" are placed in the nostrils. The affected region is defined in the gloss as "the middle of the nose as far as the back, penetrating to the region between the two eyebrows"—a description which might be an effort to define the frontal sinus region. Curiously enough the next case—"fracture in the nose"—is given an unfavorable verdict, perhaps due to the unfavorable Egyptian climate, and no treatment is suggested.

The treatise now proceeds from the nose to the maxillary region, extending to the ear at one end and the lips at the other end, and adding also the mandible. All the troubles discussed seem to be wounds and not diseases. Five of the 10 cases are wounds in the gema' (gm'), which the ancient surgeon explains in a gloss is "between the orbit (?) of the eye and the orifice (?) of the ear at the back of the jaw." Explaining the relations of the bones in this region he says in another gloss that a thing he calls the 'am 'et is the "back part of the jaw," meaning, of course, the ramus. He adds the interesting remark: "The back of the 'am 'et (ramus) is in the gema', as the claw of an 'am 'e-bird is thrust into a thing." It is evident that the ancient surgeon is likening the 2 fork-like projections on the top of the ramus (the coronoid process and the condyle) to the claws of some two-toed bird,[7] and the gema', into which this two-toed claw is thrust, is, of course, the temporal bone. We should here observe that the ancient anatomist not only noticed the resemblance of the ramus, with its claw-like fork at the top, to the claw of the bird and found it useful in his description, but also evidently drew his name for the bone from the name of the bird, thus furnishing, I believe, the earliest known example of this particular kind of terminology-building, later, and still, very common. The identity of the gema' is again revealed in a gloss on Case 7 in which our ancient writer says "the ligaments back of the 'am 'et (ramus) are fastened to the gema' (temporal bone) back of the jaw." As every physician knows, the temporal muscle which operates the mandible is anchored on the temporal bone and attached to the anterior fork of the ramus (the coronoid process). Among the

[7] If I am correctly informed, the ostrich is the only two-toed bird. The word here used is not the customary word for ostrich in Egyptian.

5 cases (18-22) of trouble with the gema' (temporal bone) it is of great interest to note the surgeon's observation of complications both in the ear and in the eye. A glance gem'=temporal bone and 'am 'et =ramus shows the layman in these matters how close are these bones to the orifice of the ear—a commonplace fact to the physician. The last of these 5 gem' cases is a fracture of the gem'; the observer notes that the patient suffers from deafness, and the surgeon is directed to clean out the ear on the affected side with a swab of linen in order to be able to see the "absorption" (?), explained in a gloss as "absorption (?) of bone tissue in the inside of the ear." This examination is in spite of the fact that the surgeon's verdict is unfavorable and that no treatment is suggested.

Two cases of trouble in the mandible are not wholly clear. Their occurrence in the treatise, however, reminds us of the extraordinary evidence in the Harvard mandible of the surgeon's skill in tapping and draining an ulcer deeply buried in the alveolar process (Fig. 9). In a case of dislocated jaw the practitioner is told how to place his hands in order to force the dislocated bones back into place.

The treatise devotes 27 cases to the head and then proceeds lower. The fourth group of cases (28-33, six in number) concern the throat and neck (cervical vertebrae). The first is a serious case of "a man having a knife wound in his throat, penetrating to his gullet; if he drinks water it turns aside, issuing from the mouth of his wound, and he is very hot and develops fever from it." Strangely enough, the physician seems to worry less about this case than about others which would seem to us less serious.

The remaining 5 cases concerning the vertebrae of the neck (29-33) again display the surgeon's desire to render his terms precise. One of these deals with a "wenekh of the vertebra of the neck." The patient loses control of arms and legs and the excretory organs and the physician gives him up. It is interesting in this connection to recall that the physicians of the Pharaoh pronounced the architect Weshptah's case hopeless. Nevertheless, although no treatment is suggested or intended, the surgeon appends an explanation for each of 3 important matters arising in the discussion of this hopeless case. The first of these is a gloss on the name of the case. It reads: "Concerning: 'a wenekh in the vertebra of the neck'—it means between one vertebra of the neck and the next one, the flesh which is upon it being whole; as one

says 'wenekh' concerning things which had been joined, when one is broken from another." It is obvious that a dislocation of the neck is meant.

Among the mechanics employed on the great building of Egypt, like the pyramids and temples, there must have been many such case. A single excavation campaign, which exhumed between 5,000 and 6,000 bodies, disclosed one person with a fractured bone among every 32 people. The last of the 5 cases of trouble in the cervical vertebrae is called "sehem in the vertebra of the neck" (Case 33). The patient is deaf and speechless and has lost all control of arms and legs. The physician at once pronounces the unfavorable (third) verdict and offers no treatment, but displays his further purely scientific interest in the case by adding 2 glosses: "Concerning: 'a sehem in the vertebra of the neck;' it means one vertebra of his neck has been depressed into the next, one penetrating into the other and not assuming any carrying" (meaning, of the weight above). The second gloss explains that this has happened because the injured man "has fallen head downward on his head, driving one vertebra of his neck into the next." From other sources we know that the word sehem means "crush" and was not an uncommon word, but the scientific interest of the ancient surgeon does not allow him to leave the case merely as that of a broken neck, designated by a common word; he desires to explain what happened.

The same purely scientific interest is displayed in discussing the very next case, which opens the next group, consisting of 5 cases (34-38) devoted to the collar bone and shoulder (clavicle and scapula). In speaking of the flesh over the collar bones and thorax the ancient writer casually adds: "There are two canals under it: one on the right and one on the left of his neck. They lead to the lungs"—a fact which evidently interested him though it had no necessary bearing on the case. The operations for a dislocated clavicle and scapula are both described. In both the patient is laid out on his back and to repair the shoulder the arms are spread out "in order to stretch out the shoulder until the dislocation falls into its place."

The sixth group contains 9 cases (39-47) concerned with the thorax. Among these it may be that one is cancer, a disease already designated as karkinoma in the late Christian documents of Egypt, as affecting the breast of a woman. All the patients in our papyrus, however, are men.

With the forty-eighth and last case the treatise passed to a seventh group, cases of the spine. The trouble affects one of the vertebrae of the back. The patient suffers pain in moving his legs. The practitioner is instructed: "He should place him prostrate and make for him . . . " We shall never know what interesting operation followed, for at this point the ancient copyist stopped in the middle of a sentence, and, as we have already noted, when he resumed copying on the back he no longer had before him the great lost medical book of which he has given us such an extraordinary glimpse. Among Mr. Smith's papers I find a sympathetic echo of the same disappointment which I felt myself on reaching this point in the document. Referring to this point Mr. Smith says: "Here ends abruptly the face of the papyrus; on the back we find 5 more pages, the work of two different hands, and the first part mere magical bosh—with five receipts of not much value."

I have intentionally given little or no attention in the foregoing brief discussion to the scanty therapeutic, a matter in which the treatise is, on the whole, not strong. In the healing of wounds and bruises the ancient physician's favorite application was fresh meat, followed after the first day by ointment of honey and an astringent herb. The complete materia medica of the document would make a surprisingly brief and simple list. The attitude of the physician is distinctly that of cooperation with nature. Repeatedly he directs the practitioner to undertake no treatment but to put the patient on normal diet and await results. This is an extraordinarily sane point of view in such an age. It should be noted also that many of these cases are solved by operation and only afterward, or not at all, by medicaments. If a man has a dislocated jaw which the surgeon has succeeded in forcing back into place, he is only to apply a simple ointment by way of soothing the soreness afterward.

The most valuable body of material in the work is the group of 70 explanations, which we have called glosses—definitions of terms contained in the discussions of the cases. Their character has already been illustrated. They are encountered at the very beginning of the preserved portion of our document and it is with the deepest regret that one finds, in mutilated condition among the fragments preceding the first well preserved column of text, a long gloss containing an account of the heart and its system of canals and vessels. This statement is, in part, a duplicate of a similar account in the Papyrus Ebers.

but in the Edwin Smith roll it is longer. It makes continual use of the word "count," suggesting that the counting of the pulses of the heart is meant, but I have not yet been able to make this conjecture a certainty. We have here the famous passage, likewise found in Ebers: "There is in it (the heart) a canal leading to every member of the body. Concerning these—if the physician . . . places the fingers on the back of the head, on the hands, on the pulse, on the legs, he discovers the heart, for the heart leads to every member and . . . it beats (literally 'speaks') in the canals of every member." In our document this extraordinary account of the heart as the center of a system, throughout which its pulsations are felt, forms an explanatory gloss appended to a case of a wound in the head—apparently in the effort to account for disturbances carried throughout the body, though resulting from the seemingly local trouble in the head. This effort to reach a scientific explanation of the observed conditions illustrates the physician's interest in the scientific aspects of his subject, which we find throughout this venerable document.

Sometimes, however, these explanatory glosses display simply a desire for greater precision. Thus in Case 8, dealing with a fracture of the skull under the skin, we have the following gloss:

"Concerning: 'a fracture in the skull under the skin of the head without there being any wound upon it';—it means: a fracture of the shell of the skull, the flesh of the head being whole."

In dealing with the case of the gash in the eyebrow we have a gloss in explanation of the bandages which reads: "Concerning: 'the two 'awy of linen';—it means: two bandages of linen. Let them be applied on the two lips of the knife wound, in order to cause that one join to the other."

The question at once arises: why were not these more precise data included in the original discussion of the case, rather than appended as a seeming afterthought? It is quite evident that the original discussion was an inherited text which, if not canonical, was sufficiently respected so that it was not to be altered by such insertions. The medical rolls of the royal physicians, brought in at the architect Weshptah's death, which we recalled at the beginning of this paper, were just about a thousand years old when our copyist was making the Edwin Smith roll. Such a text, already a thousand years old, would of course contain obsolete words requiring explanation. For

example, in Case 8 some later reader of the old document has felt it necessary to explain the injunction to operate, as follows:

"Concerning: 'the seken of the depression outward, on the side of him having this hurt';—it means: pressing the depression outward on the side of him having this hurt." It happens that another case employing the word seken, twice substitutes for it the variant "elevation." The present writer thus incidentally learned that the ancient word seken means "elevation" both as verb and noun. But even the old Egyptian reader found that the word was no longer familiar and needed definition.

Besides such obsolete words there were also old idioms which had fallen into disuse and needed explanation. We find a very interesting example often appearing in cases in which the physician waives any treatment but gives the practitioner the following instructions, which, literally translated, mean: "Put him on his fingers," or, even more curiously in a frequent variant, "moor him on his fingers." Even to the Egyptian reader of the Edwin Smith Papyrus in the seventeenth century B.C. this mysterious admonition was enigmatic. The commentator therefore supplied a gloss, reading: "Concerning: 'moor him on his fingers';—it means: to put him on his accustomed food without giving him medical treatment." This sound and conservative policy is very often recommended by the ancient physician. How it might have been possible for so grotesque an injunction as "moor him on his fingers" to come to mean "put him on his accustomed food," there is not space here to conjecture; but it may be mentioned that the ancient oriental of course ate with his fingers, and the line of connection between the curious idiom and its meaning is perhaps to be found in this custom. The student of English 5,000 years hence will doubtless find phrases about food, like "grub-stake," quite as puzzling as the curious old idiom of this medical document.

Our copyist undoubtedly found already appended to the text these explanations of the quaint or no longer intelligible words and phrases of his ancient ancestors. For these glosses are in the language of the Middle Kingdom, a period several centuries earlier than our papyrus. Our copyist was not himself a medical man, while the glosses are obviously the work of a closely observant physician. It is worth while noting that in one of these glosses we have a hint that he has not always preserved the complete text of the ancient book he was endeavoring to explain. The glosses are always quite clear in their

arrangement, introducing the phrase to be explained by the word "concerning" following which there is, therefore, a verbatim quotation from the original discussion. In the gloss on the word seken already noted, we find at the end of the phrase to be explained the following words: "on the side of him having the hurt." Now these words are not in the original discussion as it is preserved in the Edwin Smith Papyrus and they indicate that the trouble was on one side of the skull, a circumstance not elsewhere mentioned in the discussion of the case. Hence the sudden appearance of this new item in the gloss suggests that the medical book which the commentator had before him had a fuller text. It is possible, therefore, that the original ancient text out of which the glosses have grown has not always been reproduced in full. This conclusion would explain the brevity with which surgical devices obviously needing some further description are merely mentioned by name.

The reader is now in a better position for making a general estimate of these 17 columns of the front. We have here in 377 lines 48 systematically organized cases, chiefly surgical, discussing especially the bony framework of the body from the braincase downward to the thorax and the vertebrae below the cervical group. These discussions form the torso of a great lost medical book on surgery and external medicine already so old in about 1600 B.C. that commentaries on many terms and phrases had long before become necessary. This commentary, made up of 70 glosses, may already have been several centuries old when copied into the Edwin Smith Papyrus.

In bulk even this torso of the ancient book considerably exceeds the other leading medical papyri: Ebers, Hearst and Berlin. Hearst has 273 lines (and a few small fragments), while the Berlin Papyrus has 280. Both are about 100 lines shorter than the front of the Edwin Smith Papyrus alone. The stately Ebers papyrus, with its 110 columns of text, 875 recipes, and a total of 2,289 lines, although much larger, has only about 250 lines of material which can be compared with the cases in the Edwin Smith Papyrus.

In method and character the old "Book on Surgery and External Medicine" is far superior to these other 3 rolls on which we have heretofore based our estimate of ancient Egyptian medical knowledge. It is important to make this fact evident. All of the 3 papyri just mentioned, not excluding the great Papyrus Ebers, are merely haphazard collections of recipes mingled in an indescribably confused

hodgepodge; whereas our old "Book on Surgery and External Medicine" is a systematic organization and discussion of cases. While we have long known, especially from the Ebers Papyrus, that the Egyptian physicians made diagnoses, yet out of the 875 recipes in Ebers only 47 are accompanied by a diagnosis of the ailment to be cured; and of these only a group of 21 unfortunately very limited cases of boils and the like, at the end of Papyrus Ebers, can be compared in care and system with those in the Edwin Smith Papyrus. The other 2 important medical papyri contain fewer diagnoses than Ebers. The Berlin roll has only 2; and the Hearst Papyrus only 1, a very meager diagnosis of rheumatoid trouble in fingers and toes.

The same contrast is observable in the matter of systematic classification of cases by a verdict following the diagnosis. No other medical papyrus contains this system, which we find so carefully employed in the Edwin Smith roll, classifying all cases by appending one of three verdicts: favorable, doubtful, unfavorable. The third verdict is not found in any other document. The second verdict is known elsewhere only in Ebers, where it occurs twice, and the first verdict, applying to easy cases requiring simple treatment, is found sixteen times in Ebers, twice in the Berlin Papyrus, and once in Papyrus Hearst.

As for the commentary, it is found in the other medical documents of Egypt only in the Ebers Papyrus, which contains 26 glosses, not systematically following the cases to be explained, but in 2 disconnected groups which the ancient scribe, having disarranged his papers, has intruded into irrelevant discussions. To sum up this comparison, then, the other leading medical documents of ancient Egypt (Ebers, Berlin and Hearst) are each a hodgepodge of miscellaneous recipes dominated by magic from beginning to end, while the old "Book of Surgery and External Medicine," partly preserved in the Edwin Smith Papyrus, appears by contrast as a unique organization of cases containing especially in examinations, diagnoses, verdicts and glosses, more scientific medical discussion and indeed in the glosses 250% more commentary material than all the other surviving ancient Egyptian medical documents combined. We have, therefore, in the Edwin Smith Medical Papyrus, as we stated at the beginning, obviously the most extensive and important surviving source for our modern knowledge of ancient Egyptian medical science. Among the earliest known monuments in the whole range of ancient investigative science it stands easily first, to

be compared only with the famous Rhind Mathematical Papyrus in the British Museum, a book of nearly the same age.

Incomplete though it is, this torso of the ancient Book of Surgery and External Medicine preserved in the Edwin Smith roll offers enough to enable us for the first time to form a just estimate of the character and value of Egyptian medical knowledge. Each of these 48 cases is, as we have seen, identified by a list of objective conditions carefully observed—conditions often due to wounds or accident. The latter cases, due to physical causes quite clear to the physician, obviously have no connection with the activities of malignant demons of disease. Thus these cases of organs and tissues injured by intelligible physical agencies form a realm quite uninvaded by magic powers—a realm in which the Egyptian physician gathered the observable facts of anatomy, physiology, surgery, and therapeusis, quite unbiased by his inherited traditions regarding the demoniacal causes of disease.

In these 48 cases of the Edwin Smith Papyrus only one mentions or makes any use of a magic charm, and it is evidently not an accident that this case which resorts to a charm is also the only one which lacks any verdict. The physician evidently excluded it from his list of cases to be treated by other than magical means. We have here, then, a group of the earliest recorded observations in natural science made by man. Here was a realm in which the physician was confronted often enough, to be sure, by the unknown, but not by the demoniacal. Here was the physician's exclusive realm, to be dealt with by the physician's skill. He knew it and recognized it and applied to it the phrase "art of the physician," as he repeatedly calls it in contrast with the "art of incantations," [8] applied to ailments arising from demoniacal causes. The current view, that in all cases Egyptian medical practice invariably employed magic devices, a view in which I formerly also shared, is quite evidently wrong. There was, indeed, surviving from primitive times a large body of traditional practices in medical treatment wholly or chiefly magical which never disappeared. Such practices, universally and implicitly followed by the common people, forming what we may call "demoniacal medicine," always had its devotees, the descendants of the old "medicine men," with their rolls of ancient hocus-pocus, like the medical papyrus of the British Museum, or the "Charms for

[8] Without any seeming connection with the text the phrases "the art of the physician" or "the art of incantations" are to be found abruptly intruded into the prescriptions in the medical documents. It seems to me highly probable that there is an effort here to distinguish the two different agencies which the physician may apply.

Mother and Child" in the other well-known roll, at Berlin. Such primitive superstition dies hard. It lasted far down into the history of our own land. Increase Mather, President of Harvard University, in his treatise on "Remarkable Providences," insists that the smell of herbs alarms the devil and that medicine expels him. Such beliefs have probably even now not wholly disappeared from among us. We cannot wonder that this was the almost universal point of view in the early world with which we are dealing.

These essentially magical rolls, however, to which we have just referred, occasionally absorbed something of the growing medical knowledge other than the demoniacal. A very little of this leaven crept into Papyrus Hearst, more into the Berlin roll, and yet more into the famous Papyrus Ebers. But even so, the Papyrus Ebers remains a mere hodgepodge of recipes and all the treatises mentioned here were the working tools of superstitious practitioners of demoniacal medicine, who were no more truly representative of the best medical knowledge of the time than are the chiropractors, faith-healers, and innumerable other untrained quacks of our own day. The author of the great Book of Surgery and External Medicine, of which we have a mere fragment on the front of the Edwin Smith roll, was one of a group of men who will likewise inevitably have been children of their time. We cannot conceive that they ever ceased to believe in the power of magic; but they had learned that in surgery and medicine they were confronted by a great body of observable phenomena, which they systematically and scientifically collected, sometimes out of interest in the salvation of the patient, sometimes out of pure interest in the scientific truth. The class of men thus revealed to us are the earliest natural scientists of whom we know anything, who, confronting a world of objective phenomena, made and organized their observations and based inductive conclusions on bodies of observed fact. It is important to emphasize here the fact that these men evidently practiced dissection of the human body, a method of investigation in which Greek medicine, 1500 years later, was noticeably weak.

The current conclusion regarding the mind of the ancient Egyptian, a conclusion in which I have myself heretofore shared, has been that he was interested in scientific principles, if at all, solely because of the unavoidable necessity of applying them in practical life; that if he discussed the superficial content of a many-sided geometrical figure or the cubical content of a hemisphere it was because he was obliged

to measure fields for taxation purposes and to compute the content of granaries. In the field of Egyptian mathematics Professor Karpinski of the University of Michigan has long insisted that the surviving mathematical papyri clearly demonstrate the Egyptians' scientific interest in pure mathematics for its own sake. I have now no doubt that Professor Karpinski is right, for the evidence of interest in pure science, as such, is perfectly conclusive in the Edwin Smith Medical Papyrus.

While it is now quite evident that the treatises of the greatest physicians of ancient Egypt have not survived in the available medical rolls, we should notice that even the Edwin Smith Medical Papyrus, taken as a whole, is a compilation from 3 sources, 2 of which contained the commonest magical rubbish. As we have seen, however, the compiling copyist had access to one of the earlier great medical books, a stately roll of many columns. He doubtless began at the beginning of the fine old roll before him and, perhaps laying down a new unwritten roll of nearly 27 feet in length, he copied the earlier sections of the great work on Surgery and External Medicine. That filled the front side of his new roll, or carried him to its last sheet, where he left a sufficient margin of space to insure the safety of the last column and prevent it from being frayed or torn. We shall never know what occasioned the interruption after the front of the new roll was filled up. We can hardly suppose that the mere act of turning to the back of the roll could in itself have been the occasion which led the hack copyist to turn away from his great Book of Surgery and External Medicine to another roll which he had at hand—a superstitious mess of incantations, with which he, or possibly some other copyist, then began to encumber the back of our roll.

He was working for some quack who wanted nothing better than a fine line of magical wares with which to ply his daily calling in a superstitious age. This first owner of our roll was probably a little practitioner in one of the perhaps suburban villages on the fringes of the magnificent imperial capital of Egypt at Thebes. Eventually he handed on the roll to some later worthy in the same craft. The last owner was much attracted by a book containing recipes for "transforming an old man into a youth of twenty" and he took pains to copy these at the end of the older material collected by his predecessors. In the meantime, much handling and daily use of the document had frayed the beginning of the roll, and case after case of the fine old

Book of Surgery and External Medicine dropped off in tatters. When at last the village quack himself fell sick and found his art unable to exorcise the demons of disease, his surviving relatives carried him up and laid him away in a rock tomb in the great Theban cemetery. Luckily for us, they laid his roll in his coffin with him; and it reposed in perfect safety throughout the vast sweep of human history for some three and a half millenniums from the migrations of the Hebrew patriarchs and the prehistoric wanderings of the Greek barbarians to the American Civil War. The modern descendants of the old Egyptian quack, searching the tombs for salable plunder, found the roll beside the body of their Theban ancestor and saw in it prospects of gain. They stripped off its tatters of papyrus still hanging on the outside, to make it look more "ship-shape." After selling this roll to Mr. Edwin Smith in January, 1862, they patched up another out of indiscriminate rubbish and gave it the appearance of a papyrus roll by wrapping around it and gluing in place the tattered fragments which they had stripped off the genuine roll. Two months after the first sale they put this dummy roll also on the market and sold it, likewise, to Mr. Smith. Detecting the fraud, Mr. Smith recognized and rescued the new fragments of the precious medical book, thus recovering for science the extraordinary, even though fragmentary, discussion of the heart and its system of canals, to which we have already referred.

Such is the new chapter in the history of American Egyptology, begun two generations ago by the work of Mr. Edwin Smith. The papyrus which so appropriately bears his name has revealed to us furthermore a new chapter in the history of science. We have now at least an intimation of the character of the medical knowledge and practice of the great royal physicians at the Pharaoh's court in the days of the Hebrew patriarchs. These men, the leading scientists of their day, the earliest observers in natural science, and the first men to dissect the human body are thus known to us only in a later, incomplete copy of one of their books. May it some day be our good fortune to find lying in the tomb of such a royal physician the complete Book of Surgery and External Medicine from which the front of the Edwin Smith Papyrus was copied!

ANNOUNCEMENTS

Since Jan. 1, 1922, the following have been elected fellows of the Institute:

Chas. A. Parker	Walter F. Winholt
McMicken Hanchett	Ellison L. Ross
Edward A. Oliver	Thomas E. Roberts
Ernest L. McEwen	Lester R. Dragstedt

The next Pasteur Lecture will be given by Dr. Jacques Loeb of the Rockefeller Institute for Medical Research in New York.

May 10 an informal dinner was given at the University Club to Sir Thomas Lewis, who gave an illustrated lecture on the action of quinidine on auricular fibrillation.

The Board of Governors has appointed a special committee on the Medical Needs of Chicago, and subcommittees have been designated to report on otology, orthopedics, medical jurisprudence, mental hygiene, hospitals, pediatrics, oral pathology and hygiene, rehabilitation.

The joint meeting of the Institute with the Chicago Surgical Society, February 3, was addressed by Dr. C. L. Starr of Toronto; the joint meeting with the Chicago Ophthalmological Society, April 21, was addressed by Professor E. Fuchs of Vienna on ocular manifestations of internal secretions; at the joint meeting with the Society of Medical History, May 12, Professor J. H. Breasted of the University of Chicago read a paper on the Edwin Smith Papyrus, an Egyptian medical treatise of the seventeenth century before Christ.

OCULAR MANIFESTATIONS OF INTERNAL SECRETION

Prof. E. Fuchs
VIENNA

April 21, 1922

Only when preparing this paper did I become aware of how much had already been said and written about endocrine secretion in this country, which has now taken the leading part in this line.

I have followed the development of the new science from its very start. When I graduated, not even the function of the thyroid was known. The first observation of troubles, following its removal, was made, long before Kocher, in Vienna by Weiss, who described tetany as a sequela of the operation. Eiselsberg in Vienna was the first to study the function of the thyroid experimentally by removing the gland of sheep, and the books of Biedl and Falta of Vienna are standard works on endocrinology.

The ductless glands are innervated by the vegetative nervous system and act through this, not on individual organs; but on the tissues. How deeply they may in this way influence the whole organism is illustrated by gigantism due to hyperfunction of the pituitary gland. Not only the development of the body, but also character, attainments, affections, and sleep have been attributed to internal secretion. Without denying that internal secretion may play a part, I think that it is not worth while to discuss this, since there is no evidence. I shall therefore discuss only those manifestations of internal secretion which are at least probable.

If the evidence is to be conclusive, the symptoms of hypofunction, following extirpation of the gland, should be removed by the incorporation of the products of the same gland, and the administration of these to a healthy person should be followed by the symptoms attributed to hyperfunction. This requirement has been fulfilled only in a few instances and scarcely ever with regard to the eye. Even the most striking ocular manifestation of hyperthyroidism, exophthalmos, could rarely be produced by introduction of thyroid substance.

The difficulties of investigation of this subject are mainly due to two facts: First, the active substance of only two glands has been isolated, thyroidin and quite recently crystallized thyroxin from the

thyroid, and ephinephrin from the suprarenals. Abderhalden claims recently to have obtained the active substances of these and of the other ductless glands in a perfectly hydrolyzed form, which he terms opton. Second, the correlation which exists in a stimulating or inhibiting form between the individual glands make it impossible to determine whether the symptoms, following for instance extirpation of one of them, are to be attributed exclusively to it or in some part also to one of the other glands influenced by the extirpated one.

Among the methods of investigation the experimental takes the first place. The most ancient experiment dates from antiquity, showing the sequelae of castration in man and animals. The counter test to extirpation is the implantation of glands or the incorporation of gland substance in some form. Another way of evidencing experimentally the correlation between different organs is Abderhalden's method, about the reliability of which opinions are still divided.

The second means of investigation is clinical observation. The method of observation of the clinical symptoms followed by the study of the changes in the glands after extirpation or after death, is not most trustworthy. Another method of clinical investigation is the observation of the therapeutic effect of the administration of gland substance in various diseases. Modern literature abounds in articles of this sort. In this respect I agree fully with Stewart, who says that the contrast is great when we leave the desert into which the physiologists and experimental pathologists have wandered, striking many rocks, but finding few springs, and pass into the exuberant land of clinical endocrinology, flowing with blandest milk and honey almost suspiciously sweet.

The beneficial effect of drugs derived from glands is conclusive only if it has been obtained in numerous cases and with a certain amount of regularity, as for instance the thyroid treatment of cretinism. Otherwise we should bear in mind that to cases reported as treated successfully a greater number of unsuccessful cases without doubt correspond; these as a rule are not published. Again, the apparent success may be due to suggestion or to a coincidence with spontaneous relief. And even if the success in a given disease could be attributable to the gland drug, it would by no means be a proof that the disease is due to a disorder of this gland. Haskins rightly asks whether because cascarin is efficacious in relieving constipation, we should conclude that this is so because the patient is suffering from hypocascarism. The fact that

a harmful effect of glandular drugs is extremely rare and as regards the eye is known to occur only when the use of thyroid preparations is abused ought to make us cautious as to their therapeutic efficiency in general.

Contrary to much that has been said and printed on ocular troubles due to the ductless glands, the symptoms which occur so often that their relation to the glands may be said to be ascertained are few. Many of the ocular symptoms in cases of glandular disease have been observed only occasionally, so that they may be only indirect consequences of the glandular disorder, as for instance retinal hemorrhages from increased blood pressure in consequence of an excess of epinephrin in the blood. In some cases also a mere coincidence is possible. I shall also exclude mere mechanical damages, as for instance atrophy of the optic nerve resulting from pressure by an enlarged hypophysis. I shall review what is known concerning the ductless glands, summarizing their action on the eye.

1. The thyroid is supposed to act as a stimulant on the thymus, suprarenals, and gonads and as an inhibitor on the pancreas, hypophysis, and parathyroids. Thyroid preparations have only an indirect influence on the pupil as illustrated by the fact that in cases of exophthalmic goiter dilatation of the pupil by epinephrin is obtained more easily. Abderhalden asserts that his opton of thyroid together with that of testis contracts the pupil of an excised frog's eye, the only instance of miosis effected by organic drugs. The general action of the thyroid is supposed to be in the main threefold. The first is the acceleration of metabolism.

In exophthalmic goiter the metabolic rate is increased, which accounts for emaciation in spite of copious feeding. In the eye accelerated metabolism manifests itself by intra-ocular tension. Hertel showed that after intravenous injection of several cubic centimeters of a 10 per cent. solution of sodium chloride the tension of the eye drops, the increased osmotic tonus of the blood causes water to pass from the eye to the blood by diosmosis, diminishing in this way the intra-ocular tension. I used this procedure sometimes in cases of acute glaucoma with so high a tension that I apprehended an intra-ocular hemorrhage at their idectomy, and I succeeded in reducing the eye tension considerably, for instance from 60 to 40 mm. of mercury. Again Hertel stated that in animals with symptoms of exophthalmic goiter or fed with thyroid, the injected salt solution disappeared sooner

from the blood, and the intra-ocular tension took less time to rise to its former level. On the contrary, after extirpation of the thyroid the diosmotic exchange between eye and blood was protracted, and the diminution of tension after the injection of the salt solution was less or even nil. Accordingly, he found the tension in general low, in cases of exophthalmic goiter averaging 16 mm. of mercury, while in cases of hypothyroidism with myxedema the average tension was higher, between 29 and 31 mm., and in two of the cases symptoms of glaucoma were present. The latter responded to thyroid treatment by a reduction of tension, in one case from 26 to 16 mm., in the other from 40 to 18 mm. The relation between glaucoma and the thyroid is supposed to be due to the influence of the gland on the salt metabolism. In cases of glaucoma the salt in the blood amounted to 0.72%, as compared to 1.13% in healthy persons. Imre also obtained good results by thyroid treatment in glaucoma, and he found the tension lower during pregnancy when the thyroid is enlarged. Abderhalden by his method found disorder of the thyroid in cases of glaucoma.

Another effect of the thyroid is probably the destruction of toxins which are produced by the normal metabolism and poured into the blood. Animals can be immunized against the 2-to 10-fold quantity of various toxic substances by feeding with thyroid. The increase of metabolism and with it of metabolic toxins during pregnancy is counterbalanced by an increased function of the enlarged thyroid. But if this increase of function should be less than the demand the toxins might accumulate in the blood and cause general and local disturbances. In this way albuminuria as well as retinitis and optic neuritis, occurring sometimes during pregnancy, have been accounted for. But these may just as well be attributed to the action of toxins produced in excess by the enlarged thyroid. At least the cases of optic neuritis which occur following thyroid treatment for obesity point in this direction. Birch-Hirschfeld and Inouye observed atrophy of the optic nerves, together with degeneration of the ganglion cells of the retina in dogs after feeding with thyroidin, just as it can be produced also by other toxic substances such as quinine, salicylates, etc. In cases of exophthalmic goiter papilledema, optic neuritis and optic atrophy have also occurred.

The ocular symptom most regularly encountered in Graves' exophthalmic goiter is exophthalmos, but this symptom in particular is only exceptionally seen following feeding with thyroid. There is no con-

sensus of opinion concerning the immediate cause of exophthalmos, and it may even be that it is not directly dependent on the thyroid, but on some other gland influenced by the thyroid. It is especially the thymus which seems to play a part in exophthalmic goiter, and patients treated unsuccessfully by extirpation of the thyroid recovered after extirpation of the thymus.

The sequelae of hypofunction of the thyroid are well known as myxedema and cretinism, but the eye is rarely affected. Treacher Collins reports a case of myxedema in which a central keratitis developed, which responded well to thyroid treatment. Cases of cataract, choroiditis, retinal hemorrhages, and optic neuritis with subsequent atrophy, together with myxedema, are on record. After extirpation of the thyroid in man cataract and optic neuritis have been observed; after extirpation in dogs, interstitial keratitis. In the numerous cases of myxedema, cretinism, and operative removal of the thyroid, the recorded cases of eye lesion are so few that it is difficult to exclude indirect action or mere coincidence.

Successful treatment with thyroid preparations has been recorded in cases of corneal dystrophy, chronic uveitis, recurrent hemorrhages in the vitreous body, retinitis pigmentosa, and other diseases.

2. The parathyroids are said to inhibit the function of the thyroid. Their extract does not affect the pupil. We know nothing about the symptoms of hyperfunction of these glands. The sequelæ of hypofunction could be studied only after experimenters had learned to extirpate these glands separately. Before they had always been removed undesignedly together with the thyroid, so that the subsequent symptoms referred to the deficiency of both glands. Now we know that complete removal of all parathyroids is always followed by death from tetany. If enough parathyroid substance is left to keep the animal alive, the operation is followed by an increased excitability of the nervous system, by a reduction of the lime salts in the bones (rickets), and by nutritional disturbances of epithelial tissues, such as the hair, nails, teeth, and lens.

As to the nervous system, Falta observed during attacks of tetany an increase of refraction amounting to 3 to 4 diopters, attributable to a spasm of the ciliary muscle. In the optic nerve neuritis had been recorded in some cases of tetany. With regard to epithelial structures, Hanke found an edematous condition of the retinal epithelium of the iris as in diabetes, and Peters and Possek observed changes in the

retinal epithelium of the ciliary body in cases of zonular cataract, which is supposed to result from parathyroid insufficiency. It has been known a long time that zonular cataract occurs in children with bad teeth from deficiency of enamel and suffering from rickets and convulsions. The latter have been recognized as being due to infantile tetany, and at postmortem examination Escherich found the parathyroid of such children altered. So it is probable that zonular cataract also is due to parathyroid hypofunction. Hesse found symptoms of tetany in 81% of all his cases of zonular cataract, and 4 cases of zonular cataract among 41 cases of tetany. Extirpation of the parathyroids in rats is also followed by opacification of the lenses. Tetany in adults sometimes causes the development of a soft cataract, and the cataract occurring in pregnant women is likewise usually due to pregnancy tetany. So the correlation between cataract and parathyroid hypofunction is quite definite; but we do not know whether there is a direct action of certain chemical substances on the lens or an indirect nutritional disturbance by the intermediary of the altered ciliary epithelium.

According to Fleischer, cataract in cases of myotonic dystrophy is attributable to faulty internal secretion; according to Fischer presenile cataract in general is due to parathyroid hypofunction, and I. Schiotz goes so far as to attribute all cases of cataract to disturbances of internal secretion; but these are but conjectures without the slightest evidence.

3. Only the anterior glandular lobe of the pituitary gland has an internal secretion. This is supposed to stimulate the gonads and suprarenals and to inhibit the thyroid. After extirpation of the latter the hypophysis increases in size; it does so also under the opposite condition, namely, together with the enlargement of the thyroid in pregnancy. Infundibulin dilates the pupil of an excised frog's eye. Abderhalden's pituitary opton is said to promote the epinephrin mydriasis.

Hyper- and hypo-function of the pituitary gland are followed by manifold and severe sequelæ in the whole body, but no direct action on the eye is known, the affection of the optic nerves in cases of hypophyseal tumor not being due to internal secretion but to pressure. Excessive feeding of pituitary extracts to animals did not cause any eye troubles.

4. The thymus is supposed to inhibit the thyroid and gonads. Hyperfunction of the gland is presumed to be present in cases of status thymicolymphaticus and in some cases of exophthalmic goiter. The gland has been found enlarged in some of the latter cases, and its removal had a favorable influence on the disease. Implantation of thymus in animals sometimes caused symptoms of exophthalmic goiter. With the exception of eye symptoms accompanying this disease, no other correlation between eye and thymus is known.

5. The gonads stimulate the thyroid, thymus, hypophysis, and suprarenals and inhibit the pancreas. The extract of corpus luteum dilates the pupil of a frog, the extract of ovary has no influence on the pupil. As has been said, Abderhalden's opton of testis plus opton of thyroid contracts the pupil of the frog.

Direct influence of the internal secretion of the gonads on the eye was not found experimentally, nor was there any clinical evidence of this. Many of the old observations, for instance that optic neuritis or atrophy is caused by sexual excesses, are inaccurate; other assertions, like the coexistence of ocular diseases with menstrual disorders, the recurrence or deterioration of inflammation, the appearance of acute edema, etc., with each menstruation, are doubtless exact, but do not necessarily imply direct action of the secretion of the gonads on the eye. The function of the ovaries certainly plays a part in the etiology of exophthalmic goiter, but here also there is probably an indirect action through the intermediary of the thyroid. The therapeutic effects sometimes obtained by gonad extracts in diseases of the eye must probably be considered as being due only to indirect action.

Certain diseases of the eye are encountered predominantly in members of one sex only, for instance, recurrent hemorrhages in the vitreous body and the familial optic neuritis known as Leber's disease occur in young men, and tabes with optic nerve atrophy in older men. Exophthalmic goiter, interstitial keratitis, and especially chronic uveitis are more frequent in women than in men. The influence of sex cannot be denied, but it is impossible to tell whether the predisposition of the tissues of the eye to certain diseases is due to a direct action of the internal secretion of the gonads or is effected by the intermediary of other factors.

6. In the pancreas the internal secretion is attributed to the islets of Langerhans. It is supposed to inhibit the function of the thyroid, gonads, and suprarenals. Nothing is known about an effect on the

pupil, nor of the possible consequences of a hyperfunction, only the hypofunction having been recognized as the cause of pancreatic diabetes. Numerous ocular disturbances are connected with diabetes, paralysis of the extrinsic and intrinsic eye muscles, change of refraction, alteration of the retinal epithelium of the iris, cataract, inflammations such as iritis, retinitis, and neuritis and finally high grade hypotension in diabetic coma. It is probable that most, if not all, of these changes bear only an indirect relation to the atrophy of Langerhan's islets.

7. The suprarenals stimulate the thyroid, hypophysis and gonads, and inhibit the pancreas. Loewi was the first to find that epinephrin dilates the pupil in diabetic patients and in patients suffering from exophthalmic goiter. In healthy persons also dilatation of the pupil can be obtained by a free application of epinephrin into the conjunctival sac and still better by subconjunctival or intravenous injection.

Little is known about the function of the suprarenals. Complete extirpation is always followed by death. But life is preserved if only a small portion of the cortical substance is left, the medulla being completely removed. Similarly, postmortem examination of persons who during life were apparently healthy has revealed the destruction of both suprarenals except for a small portion of the cortex. The medulla was secreting the epinephrin.

Clinical evidence of increased production of epinephrin is given by increased blood pressure, which in its turn may indirectly affect the eye. The clinical symptoms of hypofunction of the suprarenals is Addison's disease. The eye is, as a rule, not affected in this disease with the exception of pigmentation of the conjunctiva recorded in a few cases. Uhthoff describes a particular form of keratitis in Addison's disease. This being to date the only case known, it does not allow a conclusive assertion of a relation between the two conditions.

No ocular symptoms attributable to altered secretion have been recorded in cases of disease of the pineal gland.

According to the foregoing, the eyes are only exceptionally affected directly by alterations of the internal secretion of the ductless glands. It may be that a relation to internal secretion exists also in the following diseases:

Osteopsathyrosis, fragility of the bones, is as a rule accompanied by a particularly thin, blue sclera. In osteopsathyrosis, as well as in osteomalacia, the amount of lime salts in the bones is diminished, which may be due to a disturbance of the parathyroids, as in rickets.

In cases of keratonus several authors found, by Abderhalden's method, a relation to the ductless gland; but there is considerable disagreement as to which glands are involved. The green color of the cornea observed in rare cases of disseminate sclerosis and of tabes may bear some relation to internal secretion. Partial alopecia is sometimes found as a consequence of hypofunction of the hypophysis. Therefore such a relation may also exist in some cases of general alopecia, which is sometimes accompanied by iridocyclitis.

Glandular disturbance may play a part in epidemic cases of hemeralopia, occurring chiefly in spring, as well as in chronic cases resulting from liver disease. In the latter a pigmentation of the retina similar to that in retinitis pigmentosa eventually develops; this has also been attributed to glandular disturbance.

Internal secretion in a wider sense of the word is not confined to the ductless glands. Every organ pours into its lymph vessels the products of its metabolism, which differ according to the tissues from which they come, and which, being ultimately effused into the blood, act through it on all the other organs and tissues of the body. To be efficient, very small quantities of this substance may suffice, as we see by the powerful influence exerted on the whole body by so small an organ as the pituitary gland. Although there is no doubt about the existence of an internal secretion in the foregoing sense, its manifestations in the individual organs are still undetermined. Besides the general action through the blood stream every organ and every tissue influences the contiguous tissues by the products of its metabolism. This mutual influence of adjoining tissues upon each other doubtlessly plays a most important rôle in embryonic development. The experimental embryology initiated by Roux has already revealed a great number of such correlations, which, as far as they concern the eye, may be reported here in accordance with the experiments by Fischel and others.

In larvæ of amphibia the epithelium of the skin contains besides the epithelial cells special cells called Leydig's cells and pigment granules, either within the epithelial cells or in special cells, the melanophores. Where the epithelium passes from the skin to the cornea, the pigment granules in the epithelial cells, the melanophores, and the cells of Leydig disappear, because they would interfere with the transparency of the epithelium and therefore impair vision. If you transplant the eye to some other place under the skin, the cells and pigment granules

mentioned will not develop in this part of the skin, or if they have already developed, they will disappear, so that the epithelium becomes like the normal corneal epithelium. It is not even necessary to transplant the entire eye; the lens or a portion of the inner tunics of the eye, even the juice of the eye, is sufficient for the purpose. This proves that we are dealing with a chemical action of one tissue on the other. The counter test to these experiments is made by removing the eye, leaving only the cornea. Then its epithelium gradually becomes like the epithelium of the skin by developing Leydig's cells and pigment granules or melanophores. This proves that the chemical substances passing from the interior of the eye into the corneal epithelium are indispensable not only for its development as a transparent epithelium, but also for the permanent maintenance of this property.

The chemical influence of the contents of the eyeball manifests itself also on the lens. The lens is formed by a circumscribed proliferation of the ectoderm, where it stretches over the eye, the stimulus to this proliferation being given by the chemical substances emanating from the ocular vesicle. Therefore in larvæ of amphibia a lens may develop practically at any part of the skin, if the eye is transplanted under it, and the size of this lens will depend on the extent of the contact between skin and eye. In these larvæ also the retinal epithelium on the posterior surface of the iris is capable of producing a new lens, if the normal lens has been removed. This is also dependent on the chemical influence of the other tissues of the eye. If the iris alone is transplanted somewhere under the skin, it does not produce a lens, but it does so if a piece of retina has been transplanted with it. That they are really chemical substances, to which is due the proliferation of the epithelial cells in such a way that a lens is formed, is proved by the fact that it is possible to stimulate by the exclusive application of certain chemical substances the retinal epithelium of the iris so as to produce a rudimentary lens, just as Professor Loeb succeeded in effecting fertilization of the eggs of sea urchins in a purely chemical way.

The influence of the chemical substances furnished by the contents of the eye is indispensable not only for the formation of the lens, but also for its maintenance. If the lens of a larva of a salamander is transplanted into another tissue, it gradually disappears by absorption, but if a piece of retina is transplanted with it, it is preserved. The absorption in the first case cannot be attributed to insufficient nutrition,

because in the normal eye also the lens is nowhere in immediate contact with blood vessels. Could it be that senile cataract is due to the fact that the chemical substances, necessary for the maintenance of its transparency, become insufficient with old age?

Evidently the facts found experimentally on larvæ of amphibia could not be directly applied to the human eye. I shall, however, describe some conditions which at least remind one remotely of what is so manifest in lower animals, and which cannot be explained except in the same way, namely, by the chemical influence of contiguous tissues on each other.

A recently formed cicatrix of the cornea is a fibrous tissue with numerous nuclei. Gradually the latter become fewer, and the fibrillæ coalesce so as to form lamellæ which ultimately may become so homogeneous that under the microscope the old cicatrix looks nearly like corneal tissue, and has also become transparent to a certain extent (clearing up of a cicatrix), a change unknown in cicatricial tissue in other parts of the body. It must therefore be attributed to the influence exerted by the adjoining structures, either the normal corneal tissue, preserved in the proximity of the cicatrix, or the aqueous humor. The first can be excluded because the same transformation into a cornealike tissue sometimes takes place in corneal staphyloma. This originates, not from the cornea, but from the iris, and the cornealike places are found only in the central parts of the staphyloma most distant from the rest of the cornea at the margin. Therefore it must be the influence of the aqueous humor and the substances dissolved in it to which the ultimate transformation of the cicatricial tissue is due.

Another change in an old staphyloma and sometimes even in very thick cicatrices of the cornea is probably caused by the opposite condition—insufficient action of the aqueous humor. In a very thick staphyloma the anterior surface has often a skinlike structure, with papillæ and a thick epithelium with superficial keratinization. This condition may be found in patients with normal closure of the lids, so that it could not be attributed to exposure and exsiccation. The skinlike structure of the corneal epithelium must therefore probably be accounted for in the same way as the transformation of the corneal epithelium into ordinary epidermis after removal of the eye in amphibial larvæ. We may assume that in a thick staphyloma with its dense tissue the aqueous humor, diffusing into the staphyloma, does not reach the epithelium in sufficient quantity to maintain its normal condition.

The foregoing experiments on the lens of amphibia have their analogy in the human eye. After the removal of the lens, out of its capsule, for instance after the extraction of a cataract, some lens matter always remains at the equator of the lens and even grows by proliferation of the capsular epithelium. This is an attempt to regenerate the lost lens, a process which progresses much farther in animals than in the human eye, where only a thin ring of lens substance develops, called Soemmering's ring. This, however, remains there for a lifetime, and a complete absorption of the lens never takes place. On the other hand, if the lens is transplanted under the conjunctiva, as sometimes occurs incidentally in cases of subconjunctival rupture of the sclera, not only is no attempt at regeneration made, but the lens is gradually completely absorbed. This is contrary to what one might expect, the nutrition of the lens imbedded in the vascular tissue of the conjunctiva being better provided for than in its normal place where no vessels get near it. Here it is under the influence of the substances secreted by the retina and uvea, which are absent in the lymph of the conjunctiva.

Another instance is the formation of hyaline membranes within the eye. In the normal eye, Descemet's membrane, the lens capsule, and the basement membrane of the choroid are homogeneous membranes, supposed to be sort of cuticula produced by the cells that are lying on them. Defects in these membranes may be filled in by a new hyaline membrane after proliferation of the cells, by which process the new membrane is furnished. Sometimes such membranes form also in other places. In old cases of iritis the iris is sometimes covered by a homogeneous membrane like Descemet's membrane. From the pigment epithelium hyaline membranes also originate sometimes. It reminds one of a sclerosed vessel, in which quite a number of new elastic membranes often develop within the connective tissue which lies on the inner elastic membrane. Just as these elastic membranes are formed under the influence of the blood, the hyaline membranes in the eye develop under the influence of the substances dissolved in the aqueous and vitreous humor.

THE VALUE OF QUINIDINE IN CASES OF AURICULAR FIBRILLATION AND METHODS OF STUDYING THE CLINICAL REACTION

INTRODUCTORY AND HISTORICAL

THOMAS LEWIS
University College Hospital, London
May 30, 1922.

I propose to deal with the action of certain cinchona alkaloids on the heart, with special reference to the clinical condition termed fibrillation of the auricle. The alkaloid claiming chief attention will be quinidine, though something will be said of two allied alkaloids, quinine and hydroquinidine.

The original discovery of quinidine as a remedy for auricular fibrillation has been, so far as I am able to judge from published accounts, one of those happy accidents which at rare intervals help the progress of medical knowledge. But this statement, if it is not to convey a wrong impression, needs to be qualified. That quinidine would have been discovered as a remedy for fibrillation of the auricles by unaided therapeutics is in high degree improbable. The time was ripe for the discovery; it was ripe because irregular action of the heart had been analyzed into its several distinct forms, forms named and recognized the world over.

Consider the frequence with which the human auricle is and has been affected by this disorder fibrillation; consider also the tens of thousands of patients who have received doses of cinchona alkaloids, adequate to produce the change from the disordered to the ordered rhythm, and it becomes inconceivable that this change had not happened many times before Wenckebach specifically drew attention to it. It is the more inconceivable since cinchona has for very many years obtained a vague but quite uncertain reputation as a cardiac tonic.

Given a profession still unable to differentiate between one form of irregularity and another, unable to distinguish between the pulse disordered by fibrillation and the pulse scarcely disturbed by slight changes of respiratory vagal tone, and that profession would have remained ignorant of the profound effects which quinidine exerts on the heart in a special group of cases. It is when we consider the question historically,

and from this aspect, that we are able to grasp what I think it is important we should at once grasp, that this discovery was made possible only by experiment on the hearts of lower animals and by the forthcoming analyses of clinical irregularities. The very fact that we owe these remedies primarily to Wenckebach, whose work in this analytical field is for all time classical, speaks for itself. Wenckebach [1] wrote of quinine. In two patients, the subjects of paroxysmal fibrillation, he observed beneficial effects to follow the administration of this alkaloid; it does not appear that Wenckebach gave this drug expecting an action antagonistic to fibrillation. He gave this and many other drugs having diverse actions; only digitalis bodies and quinine, the latter in a very small proportion of the cases, showed beneficial action. The old and oft-repeated statements that cinchona is of value as a cardiac tonic brought no progress; unaided they could bring no progress. In 1914, Wenckebach discriminated. He named the drug as bringing fibrillation of the auricle to an end.

It was his stated wish for further trials in this specific direction that prompted von Frey's work [2] in 1918. Von Frey used not only quinine, but also its isomer quinidine and other related alkaloids, and from him came the important statement, first, that quinidine is of this series the potent alkaloid, and, second, that it will abort not only short-lasting paroxysms but also long-continued fibrillation. Von Frey's statements were soon confirmed by von Bergmann [3] and by others.[4] In the last two years favorable reports have begun to issue from many countries; in America, through Levy; [5] in my own country, through Drury and Iliescu.[6]

Fully to appreciate this discovery, our conclusions in respect to fibrillation a few years ago are to be remembered. Generally recognized to be the commonest or the only common grave disorder of the heart beat, it was known to display itself in two forms: in the form of short paroxysms, lasting a few hours or a few days, and much more often as a malady persisting until death. The view was held that if auricular fibrillation had lasted ten days, it was a settled thing. There

[1] Wenckebach: "Die unregelmässige Herztätigkeit," etc., 1914, pp. 125 and 128.

[2] von Frey: Berl. klin. Wchnschr., 1918, 1, pp. 459 and 849; Deutsch. Archiv. f. klin. Med., 1921, 136, p. 70.

[3] Bergmann: München. med. Wchnschr., 1919, 66, p. 705.

[4] Boch: Mediz. Klin., 1921, 17, 1052. Boden and Neukirch: Deutsch. Arch. f. klin. Med., 1921, 136, p. 181.

[5] Levy: Jour. Am. Med. Assn., 1921, 76, p. 289.

[6] Drury and Iliescu: Brit. Med. Jour., 1921, 2, p. 511.

were, it is true, a few very isolated cases (like that of Lea[7]) in which it passed away after lasting a longer time; but the statement still holds that once established for a few weeks, the prospect of its spontaneous passage is beyond reasonable expectation.

Consider briefly its effects: It paralyzes the action of the auricles, it wholly abolishes the regularity of the natural pulse, two effects, each of which hampers the circulation in some measure; but it has a third and more malign influence, it lifts the rate of the beating ventricle. The average rate in man at rest is 70 to the minute, in the disordered state the average and uninfluenced rate at rest is about 90 to 100 beats per minute. In quiet walking exercise the normal rate may be 80 or 90 to the minute; in fibrillation the corresponding figures are roughly speaking 130 to 150 to the minute. It is the uncontrolled state of the heart in exercise which constitutes the most serious feature of fibrillation. Thus, fibrillation throws on the heart a greatly increased burden, a burden which the weakly heart often finds beyond endurance. Because fibrillation of the auricles so upsets the balance between the calls to work and the power to work, because failure with congestion so often follows in its train, it has come rightly to be regarded as one of the outstanding phenomena of cardiovascular maladies. It is on this condition that quinidine exerts its beneficial action, restoring the normal rhythm to hearts which have beat irregularly for months or years. The drug as now usually administered is given in repeated doses of 0.2 to 0.4 gm., the allowance being from 1 to 2 gm. per diem. The change may come on the first day, it may be delayed for several or many days; but it can be produced in about 50 per cent. of all cases so treated. To the question of dosage I shall return in more detail; meanwhile, it will be convenient to study the clinical effects more closely; and in doing so I shall first describe methods of observation recently introduced.

METHOD OF INVESTIGATION

The change from auricular fibrillation to normal rhythm may be recognized by those familiar with the disordered heart action without the aid of instruments; the same event may be recorded graphically by the polygraph. The electrocardiograph, as usually employed, gives further information. It provides a general notion of the events which are happening in the auricle which is coming under the influence of

[7] Lea: Heart, 1918-1920, 7, p. 47.

quinidine, events premonitory to the actual change of mechanism. A fall in the rate of the auricular oscillations and an occasional intermediate phase of "flutter" have been reported by von Frey, who used this method. But electrocardiography as generally employed is not so suitable as a method recently introduced. To study the effects of quinidine on the fibrillating auricles, the oscillations must be recorded in as pure a form as possible; this is not accomplished by leading from the limbs, for the curves are then complicated by fine movements in the corresponding somatic muscles, but by leading directly from the chest wall in the neighborhood of the right auricle, as Drury and Iliescu have shown.[8] This method was first used by Drury and Iliescu [6] in studying the action of quinidine on the auricle, and has now become the routine practice of my laboratory. By means of this near lead, records can be obtained of the oscillations in a sufficiently pure form to permit counting, without the introduction of material error. The records give an accurate measure of ventricular rate and its variation, and a sufficiently accurate measure of auricular rate and its change.

The rate of the main auricular oscillations, those which correspond to the circus movements, in clinical fibrillation averages 450 per minute; the actual rates for individual cases are usually near this average rate, but in occasional cases the rate may be as high as 620, or it may be as low as 380 per minute. For any given case the rate of oscillation is remarkably constant over long periods, providing that uniform conditions of observation are maintained. So far as has yet been ascertained, conspicuous alterations of rate are produced only by the administration of certain drugs, though on relatively infrequent occasions there are changes of rate which are imperfectly understood. This constancy of rate under resting conditions has its value to us, for it permits us to obtain clearer pictures and comparisons of changes produced by drugs.

REACTION AND DOSAGE

Single Doses.—Let us consider first the effects of single doses of quinidine, a dose such as 0.8 gm. of the pure dried base. Such a dose invariably induces a profound reaction, beginning usually half an hour after the drug is swallowed enclosed in a thin gelatine capsule. The auricular rate falls steeply and reaches its minimum usually in 2 hours after the drug's administration. But this minimum rate is not maintained; very soon recovery begins. This is slow, being spread over 24

[8] Drury and Iliescu: Heart, 1921, 8, p. 171.

to 30 hours. Eventually, it is complete, the original rate being reached. Meanwhile, as von Frey noticed, the ventricular rate has been raised; it rises simultaneously with the fall of auricular rate, rises steeply and recovers slowly. The total fall of auricular rate is of 150 or 200 beats per minute, the level reached being in the region of 300 beats or less per minute. The total rise of ventricular rate is variable; in some cases it is comparatively small, in others it is conspicuous, and such rates as 140 or even 160 are reached. The recovery from quinidine is due to the drug's elimination by the kidneys. The alkaloid appears first about 2 hours after its administration and continues to be excreted for many hours in large quantity; traces may be found 24 hours after the administration, but that is not the rule. These statements are based on qualitive tests with Mayer's reagent (mercuric iodide 13.546 gm.; potassium iodide 49.8 gm. and a liter of distilled water). In an acid urine, containing the alkaloid, a dense white precipitate is formed by a drop of the reagent. (For further information on the output of cinchona alkaloids see Wiechmann.[9])

The constancy of these reactions in a given patient may be displayed by repeating them, allowing a sufficient time for recovery to elapse between the doses.

Increasing Doses.—That the extent of the reaction depends on the dose is easily proved by the administration of increasing doses at suitable intervals. Thus, if single doses of 0.2, 0.4 and 0.6 gm. are given on alternate days, the fall of auricular rate increases by approximately equal increments; it is to be observed, however, that 0.4 gm. gives less than double the fall produced by 0.2 gm.; the falls begin from a common baseline, recovery being complete in the intervals between the doses.

Repeated Doses.—But there is a limit to these regular reactions; an increased dose will not produce indefinitely a correspondingly increased fall. Such at all events seems to be the inference from observations of a slightly different type. If a single dose of 0.6 gm. is given and a second and like dose is administered at such a time that the fall produced by the second dose should begin when the reaction of the first dose is at its height, an equal second fall is not obtained; it is a fall of much less extent.

Similarly, if doses of 0.4 gm. are administered at intervals of 3 or 4 hours during the day, the initial fall of rate is rapid and progressive; but there comes a time in many patients when the rate becomes station-

[9] Wiechmann: Ztschr. f. d. ges. exper. Med., 1919, 7, p. 155.

ary or almost so, falling a little at each dose and rising a little subsequently. To drive the auricular rate lower, an increase in quantity may be necessary, a dosage of, say, 0.6 gm. at 4-hour intervals. Even so, stationary rates may be seen. There is a limit to the quantity which may be given safely at single doses, and the failure to obtain further slowing with high dosage is one of the reasons why, in using quinidine therapeutically, treatment has sometimes to be abandoned.

The desired result, a return of the normal heart rhythm, occurs after variable quantities of the alkaloid have been administered. In some patients a single dose of 0.6 gm. produces a steep fall which ends in the abrupt cessation of fibrillation. Much more frequently the change is obtained by using repeated doses of 0.4 gm. given every 3 or 4 hours each day. The change comes, if it comes at all, usually when the auricular rate falls to such rates as 300 or 250 per minute. In giving repeated doses it is not always necessary to force the rate below such levels; maintenance of the rate at these levels often suffices, the change to normal rhythm coming unexpectedly at any time during the continuance of such treatment. But it is necessary to allow no escape from these rates. The resumption of the natural heart beat does not occur during the phase of recovery from quinidine. Recovery, as we have seen, occurs with some speed, owing to the quick elimination of the alkaloid; as Drury and Iliescu have pointed out, if 3 or 4 doses of 0.4 gm. are given in the day, the rate will fall progressively for that day; but the curves obtained next morning will show that the effects of the drug are rapidly subsiding; the next day's treatment therefore does not start from the last night's level, there is some leeway to make up. To counteract this loss to the reaction, one or more similar doses may be given during the late hours of night or early morning. Clearly, the actual doses and times of administration are best controlled by studying the records obtained as treatment proceeds.

It has been said that a single dose of 0.6 gm. of the drug may suffice; in other cases, repeated doses, varying up to total quantities of 10 or 15 gm., may be needed. The precise limits beyond which it is unwise or unprofitable to proceed are still largely unknown.

SOLUBILITY OF PREPARATIONS

Comparisons have been made between salts of quinidine possessing widely different solubilities. We have used test doses of the sulphate, bisulphate, and bihydrochloride, the respective solubilities of which are

1 in 100, 1 in 7 and 1 in 3.6 of cold water. There is no material or constant difference in the time relations or in the extent of the corresponding reactions. When there is any small time difference in the reactions, these do not occur necessarily in the order of solubility. Thus, the bisulphate reaction is most delayed. The same statement applies to a comparison of the base and its salt. All appear to be rapidly converted into a hydrochloride salt in the stomach, and to be absorbed with essentially the same rapidity. Solubility becomes therefore a question purely for convenience in prescription, when it is desired to give the drugs in fluid form; it is actually our practice to give the drug in thin gelatine capsules.

REACTION TO ALLIED ALKALOIDS

Only two of the allied alkaloids will be discussed here. Quinine, the alkaloid first used by Wenckebach, was reported by von Frey to be less potent than quinidine, and other writers, though not all, have agreed with him. The reason for disagreement probably is twofold: 1. Commercial preparations of the alkaloid often contain very large percentages of impurities and these impurities influence the result. 2. The potency of an alkaloid is gaged by the quantity needed to restore the normal rhythm. Now this quantity varies, not only with different alkaloids but with the same alkaloid, and with the same alkaloid administered to one and the same case. Consequently, comparisons of potency undertaken by the method which has been used for uncertain, and they must remain so unless large numbers of patients are treated alternatively with the two alkaloids to be compared.

There is a quicker method, that which we have recently employed, namely, the use of fixed test doses and a comparison of the falls of auricular rate. Using this method, we find that von Frey's statement is true. Quinidine is weight for weight much more potent than quinine —the fall given by 0.6 or 0.8 gm. of the latter, as compared with that given by quinidine, is often inappreciable and rarely amounts to one-fifth of that which follows a similar dose of quinidine. The same method of comparison has been used in the case of hydroquinidine; this alkaloid has been tested because it is the chief alkaloid contaminating commercial quinidine preparations; to purify quinidine from hydroquinidine is not an easy matter and, so I am told, has but recently been accomplished with any considerable measure of success. A comparison of the action of the two alkaloids is therefore a matter of some consequence from

the commercial standpoint. Actually, it is found that the two alkaloids have a very similar potency, hydroquinidine being if anything a little the more powerful.

SIMULTANEOUS DIGITALIS THERAPY

It has been stated on more than one occasion that digitalis interferes with the reaction to quinidine and that the two drugs should not be given simultaneously. Comparisons of the fall of auricular rate obtained by quinidine, before and after the administration of digitalis in full therapeutic doses, usually show small differences. The original auricular rate is, generally speaking, a little higher when the heart is under treatment with digitalis; the fall in quinidine is usually as great or almost as great, though it does not usually reach quite so low a level when digitalis has been given; in some comparisons, too, the fall of rate has appeared to be delayed by digitalis; in others, a more decided lessening of the fall has been noticed. A striking difference in the two reactions is not the rule; such differences as exist do not seem often to be of consequence, and we think that the antagonistic action of digitalis has been exaggerated. In one patient in whom a change to normal rhythm was repeatedly obtained with a single dose of 0.6 gm. of quinidine (0.4 gm. failing to produce the transition), the same dose was effective after the patient had been fully digitalized. The simultaneous administration of digitalis has a great advantage, for it keeps the ventricular rate at a comparatively low level throughout the quinidine reaction, and one source of trouble is thereby removed. A course of digitalis immediately preceding the use of quinidine, or a lighter course actually simultaneous with the quinidine, seems often to be indicated rather than contraindicated; it may be necessary to give rather heavier doses of quinidine in these circumstances, but the control of ventricular rate is in many patients a factor of advantage with which we can hardly afford to dispense. At all events, the simultaneous administration seems to us to deserve a further and more extended trial in patients predisposed to give high ventricular rates.

ADVERSE EFFECTS AND PRECAUTIONARY MEASURES

A number of undesired toxic effects have been noted during the administration of quinidine in cardiac cases. Many of these are unimportant. Giddiness, a sense of fulness in the head, or actual head-

ache, are not uncommon; griping pains in the abdomen followed by loose evacuations are apt to occur when large single doses are given. Repeated doses may be followed by urticaria.

Palpitation.—The ventricular rate rises after quinidine, and not uncommonly reaches 120 to 160 per minute; it is part of the reaction and may disturb the patient. A rate of 160 would no doubt on occasion contraindicate the further administration of the drug. That would be the case when the onset of congestion threatened—cases which we regard as in general unsuited to the treatment. In a few cases, if dosage is carried far, the auricular rate may fall toward 200 per minute. When this happens a more serious accident may happen: the auricle is now in a state of relatively pure flutter, and the ventricular rate may spring abruptly to the full rate of the auricle (Drury and Iliescu and von Frey). The development of auricular rates below 250 or 240 per minute appears to me to contraindicate further dosage, if the rate of the ventricular rate has already risen much above 100. In cases of this kind, and of high ventricular rates generally, a combination of quinidine and digitalis is preferable.

Under quinidine, extrasystoles arising in the ventricle are frequent. Usually isolated, they sometimes occur in groups, and in a few cases a regular tachycardia may be started in the ventricle. The precise meaning of this interesting phenomenon is not known, but tachycardia of ventricular origin is so closely allied to graver disorders of the ventricle, that the appearance of multiple extrasystoles should be a signal to cease the administration of quinidine.

Idiosyncrasy to Quinidine.—A few patients exhibit a serious intolerance for quinidine. Of these I have no personal experience, but von Frey has reported cases in which after a small dose of quinidine sudden loss of consciousness with standstill of respiration has happened. Recovery occurred in his cases, but it is clear from his account that the condition is a very serious one. It is from this experience that the custom has arisen of giving first a small trial dose of 0.2 gm., following this after 24 hours by a single dose of 0.4 gm. The treatment is begun on a subsequent day. Whether this method of small trial doses will eliminate danger from this source remains for the future to decide. It is to be remarked that accidents of the kind are rare.

Dangers of Embolism.—Many years ago I witnessed for the first time a curious and fatal accident. It occurred in a woman suffering

from mitral stenosis and heart failure.[10] This woman acquired an attack of fibrillation of the auricles which lasted for several days and then suddenly ended; when it ended, clots were detached from the heart, which produced multiple embolism of the lungs and brain, and these led quickly to a fatal termination. Fibrillation of the auricles predisposes to clotting in the auricular appendices. Antemortem thrombi are found in patients dying of heart failure more frequently if the auricles were fibrillating at the time of death. Thus, in 76 postmortems on patients dying of chronic heart disease, in which clots were specially sought, I found them in 8 cases out of 23 in which fibrillation was present in the last illness and in only 4 cases out of 53 in which the mechanism had been normal. But embolism due to detachment of these clots does not appear to be more common when fibrillation exists than when the action is normal. While fibrillation predisposes to clotting, the normal auricular action favors the detachment of such clots. In treating patients with quinidine, these facts should be borne in mind; because we have borne them in mind, we have seen no instance in which the resumption of the normal rhythm under quinidine has led to embolism; others have been less fortunate.

When there is much dilatation of the heart, as indicated by congestion of the veins and liver, the therapeutic use of quinidine is contraindicated. In cases in which there have been symptoms or signs of recent embolism, the use of the drug invites disaster. From embolism there is not much to fear, providing those chosen for treatment are judiciously selected; but it is to be observed that the peril of embolism precludes the use of quinidine in cases of fibrillation in which the circulation is embarrassed. It sets another limit to its usefulness.

In paroxysmal fibrillation, a fear of embolism should not deter us from giving quinidine. The paroxysm will cease spontaneously after a while, and clotting is the more likely to occur the longer the attack lasts. Theoretically, if quinidine will bring the attack more speedily to a close, the chances of clotting and subsequent embolism will be diminished.

THERAPEUTIC VALUE OF QUINIDINE

The percentage of cases in which quinidine, as it is used at the present time, will restore the normal rhythm in the fibrillating auricles is approximately 50%. With these figures, drawn from previous

[10] Lewis: "Clinical Disorders of the Heart Beat," 1916 (3d edit.), p. 95.

records, the experience of my own clinic agrees. The figure applies to chronic fibrillation of the auricles.

When in a case of auricular fibrillation the normal rhythm is restored, the gain to the patient is considerable. It is not so apparent while the patient lies in bed, for in the cases most suitable for treatment there are few or no symptoms at rest. It is when the patient goes about again and undertakes his daily duties that he feels real benefit; and the benefit is chiefly due to the heart being once more under strict nervous control. In particular, exercise no longer raises the rate to levels which are incompatible with comfort or which produce actual distress. The change brings similar benefits to the heart as does the lowering of ventricular rate by digitalis; quinidine has the advantage, however, in patients in whom its effects are permanent, in that it frees them from further drug treatment. In treatment by digitalis the drug has to be maintained, in most cases indefinitely.

Nevertheless, the usefulness of the drug from the clinical standpoint is limited. It is limited by the high percentage of failures (50%) to restore the normal rhythm. Too much emphasis should not be laid on these failures, however, for it seems probable that the percentage will be reduced as further experience is gathered.

It is limited also by its unsuitability in cases of venous stasis. But the chief limitation is more serious and consists in the early and frequent resumption of auricular fibrillation. In not a few patients, the restored normal rhythm lasts only a few days or a week, and fibrillation returns again and again after successive periods of treatment. In others, the normal rhythm is maintained for a few weeks or months; a few cases have been observed in which it has been maintained for six months or a year. In the last group it must be judged an unqualified success, but in proportion as from case to case the return of fibrillation is less delayed, so the remedy becomes less practicable as a remedy. The value of quinidine has so far been greater in adding to our knowledge of fibrillation of the auricles than it has been in therapeutics. It has taught us many important facts, among the most notable being that the hearts which display chronic auricular fibrillation are capable of beating normally, a quality hitherto in doubt. It has also taught us that the cause which predisposes to fibrillation, or at first initiates fibrillation, is maintained in the chronic state. Although it seems clear both from experimental and clinical observation that fibrillation once established tends to maintain itself, it is no longer possible to accept the

conclusion that once established it will perpetuate itself indefinitely, though its original cause is removed. The pronounced tendency for the disorder to recur is opposed to any such conclusion; it teaches us that we have still to seek the ultimate causes of the disorder and that the prospect of fully successful treatment is along those lines of investigation.

As in our early publications, my collaborators and myself still deprecate the general use of the drug. At the present stage of investigation it should be employed only under strictly controlled conditions; it is a treatment emphatically for the wards rather than for use in an outpatient department.

THE EXCHANGE OF SUBSTANCES THROUGH THE CAPILLARY WALL

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The capillary wall is, as you know, made up of a single layer of very thin, flat cells, joined together at their edges to form the endothelial tube. Recent researches, undertaken in my laboratory, have shown conclusively that there are special muscle cells on the outside of the capillary tube and enclosing it in a kind of contractile network. When these cells contract strongly the endothelium is folded, and when they relax it requires an exceedingly low pressure only to stretch it and make the cells much thinner. The total surface available in certain tissue at a given moment for exchange of substances depends on the number of capillaries which are open so as to admit blood and on the degree of dilatation of these.[1] A definite regulation of the available surface and blood supply so as to correspond to the requirements of the tissue has been shown to take place.

The exchange itself appears at first sight to be a very complex function. A large number of substances may pass from the blood to the tissues and vice versa, and the direction and rate of exchange seem to be governed largely by the needs of the tissues, so that very generally the power of selective secretion is ascribed to the endothelial cells. I am of the opinion, however, that it is the duty of a physiologist in a case like this to try to determine what can be accomplished by simple physical and chemical forces like filtration and diffusion, and to resort to the unknown forces of the living cell only in cases in which the others are obviously insufficient.

Instead of giving exact definitions at this stage of the word "secretion" and its counterpart "physical and chemical forces," I think I can make clear the meaning by giving two examples from the domain with which we are dealing.

The first example is the supply of oxygen to tissues, and especially to striped muscles, during rest and work. It is easy to demonstrate that oxygen molecules can travel by diffusion through living tissues in the same way as they can travel through water or gelatine, and it has

[1] A detailed account of the motor functions of capillaries and of the subject matter of the present lecture is given in my book: The Anatomy and Physiology of Capillaries, Yale Press, 1922.

been found possible to measure the rate of diffusion which is in muscular tissue only about half the corresponding rate in 15% gelatine and 40% of the rate in water. It can be shown, further, that diffusion is quantitatively sufficient to supply the oxygen required by muscles in all possible conditions of rest and work, so that we have every reason to assume that the capillary wall like the rest of the tissue is simply permeable to oxygen and does not in any way actively further its passage.

The second example is the classical one brought forward and discussed by Heidenhain in the nineties. The milk of a cow contains 1.7 gm. calcium per liter. The blood contains only 0.18 gm. An enormous concentration of calcium takes place during the passage from the blood to the milk, and there can be no doubt that this is an example of secretion, of active transport by living cells; but, and this is the point I wish to make, it is not necessary to assume that any part of this active transport is accomplished by the capillary endothelium. If we assume only that the gland cells will take up from the extracapillary spaces all the calcium ions offered to them, the concentration of calcium in these spaces will be constantly lower than in the capillaries, and calcium ions will diffuse out from the blood in consequence. To explain the secretion, at least qualitatively, it is only necessary to assume that the capillary wall is freely permeable to calcium ions.

We have good reasons to believe that the normal capillary wall is freely permeable to calcium ions and, in fact, to all crystalloid substances. It is shown every day in thousands of experiments. When crystalloid drugs of the most varied kinds are introduced subcutaneously, they pass almost instantaneously into the blood, and special experiments have shown that they come in, not by way of the lymph, which would be at best a very slow procedure, but directly through the endothelial walls of the capillaries. When, on the other hand, any crystalloid substance is introduced directly into the blood, it passes out rapidly into the serous fluids and the lymph; and the concentration will reach or at least approach equilibrium.

Different substances pass through the endothelium at different rates, and these rates are, roughly at least, proportional to the rate at which the same substances diffuse through gelatine or pure water. This has been shown by Clark for several salts and glucose and by Schulemann for a large number of dye substances.

Schulemann has shown, further, that colloidal dyes will not generally pass through the walls of capillaries, and, with a few notable exceptions —the capillaries of the liver and of the intestinal mucous membrane— the capillary wall can be taken to be normally impermeable to colloids. The normal blood colloids, the proteins, do not get out into natural or artificial edema fluids so long as the capillary walls are normal; and, if colloids are introduced subcutaneously or into the peritoneal cavity, they disappear slowly and get into the blood by way of the lymphatic system.

The impermeability of the capillary wall to colloids is responsible, as shown by Starling many years ago, for the power of the blood to absorb water (isotonic salt solution) from the tissue spaces. Since the capillary walls are permeable to water and the pressure of the blood in them is higher than the extracapillary pressure, there must be a tendency to filtration of water (salt solution) out into the tissue spaces; but this tendency is counteracted and generally overcome, as shown by Starling, by the osmotic activity of those constituents of the blood to which the wall is impermeable.

Starling put blood into osmometers with tissue membranes impermeable to proteins but permeable to water and crystalloids, and found that equilibrium between the filtration and the osmotic activity of the proteins was attained when the level of the inside fluid was about 500 mm. above the outside level, the osmotic pressure of the blood proteins amounted to about 500 mm. of blood.

Since the publication of Starling's paper, osmometers for colloids have been improved repeatedly, and a considerable number of determinations made; but nothing essential has been added to the general conception. A research is in progress in my laboratory which seems to promise something, but so far the results can only be considered as preliminary.

We started from the idea that the colloid molecules or aggregates responsible for the effective osmotic pressure are possibly of different size, that some might be so small as to be held back and be able to exert their osmotic influence only in capillaries of low permeability, while others might be large enough to maintain an osmotic pressure even in very permeable capillaries. To test this point we have made determinations of the fractional osmotic pressure of blood in collodion tubes of graded permeability. We use at present 4 different types of collodion tubes, of which the A type is just on the verge of permeability to gum

acacia molecules, while B is just impermeable to all the blood proteins. Through D, sugar molecules will pass with some difficulty, while C occupies an intermediate position nearer to B than to D. These membranes can be characterized to a certain extent by their filtering capacity for water at a constant pressure. The filtering capacities and the average results of osmotic determinations on the blood of the frog, the rabbit and man are given in the table.

FILTERING CAPACITIES AND OSMOTIC DETERMINATIONS ON BLOOD OF FROG, RABBIT AND MAN

Osmotic pressure, mm., water:	A	B	C	D	% Protein
Filtering capacity.....	3	0.9	0.2	0.04	..
Frog	30	55	55	125	33
Rabbit	245	275	295	333	53
Man	very low	455	475	(710)	60

This table bears out the general hypothesis of osmotically active particles of different size. We find, for instance, for frog's blood that 30 mm. of osmotic pressure are due to particles larger than gum-molecules, while $55 - 30 = 25$ mm. are due to smaller molecules, which are all larger than the smallest protein molecules. In the frog's blood there are apparently no particles of such a size that they can pass through a B membrane but are held back by C, while such particles exist, though in a small amount, in the blood of the rabbit and man. I am not going to put much stress, however, on the differential figures until more data have been collected.

The osmotic pressures obtained in the B tubes must be due mainly to the proteins, and on this basis I have calculated in the last column the average osmotic value of the blood proteins of these different species. You will observe that they are rather different; and we have found, moreover, that there are considerable individual differences within one and the same species, so large in fact that indirect calculations of colloid osmotic pressure from protein determinations are always invalid.

We have now to consider the other factor responsible for the exchange of water between the blood and the tissue spaces: the capillary blood pressure, on which depends the rate of filtration of water from the capillaries into the tissue spaces. A fairly large number of determinations of this pressure have been made on the skin capillaries of man, but they are extremely divergent and, being obtained by indirect methods, more or less unreliable.

I am fortunate in having at my disposal a small number of determinations which cannot be challenged on methodical grounds. Miss Carrier (Berkeley), working in my laboratory, found it possible to introduce the fine point of a glass tube containing a little saline directly into a capillary and to observe under the microscope whether the pressure of the fluid in the tube was sufficient or just insufficient to prevent the entrance of corpuscles into the glass tube. Utilizing this method, the blood pressure in human skin capillaries could be determined accurately within $\pm$ 1 cm. of water. It was found to be remarkably constant in the same individual, while the pressures measured in a few normal individuals varied only from 4.5 to 7.5 cm. water. These low pressures are observed, however, only when the capillaries in question are at the level of the heart or above that level. At lower levels we have in addition the hydrostatic pressure of the column of venous blood from the point studied up to where the veins enter the chest.

When a series of measurements are made on the hand of a person at different positions below the heart, a very good agreement is obtained between the observed pressures and those calculated from the positions, except at the lowest possible positions, where the observed pressures usually fall short a little of the calculated. This discrepancy is usually pronounced when measurements are made on the foot. In the foot of a standing person, the capillary blood pressure should amount to about 1.2 m., but it is often as low as 0.7 m.; and if the subject walks a few paces, it drops down to a few centimeters. When the body is kept absolutely quiet, the pressure will rise up to the value to be expected theoretically, as shown by Hooker.

The mechanism by which movements are able to reduce the pressure of the blood in the capillaries and veins is the so-called venous pump, an arrangement of valved veins in and between the muscles which become compressed by the contraction of muscles. These veins can be emptied only in a central direction and become filled again from the periphery, and their alterate compression and relaxation will therefore pump out the blood from the periphery.

When this pump does not act or even when it acts occasionally and feebly, as in a person standing quietly erect, the pressure of the blood in the capillaries of the feet and lower part of the legs becomes higher than the effective osmotic pressure of the blood, and filtration of fluid from the blood into the tissue spaces takes place accordingly: there is a conspicuous progressive swelling of the feet.

In large animals living on land the capillaries in the lower parts of the body must often be exposed to a high blood pressure, and I believe this is the biologic reason why such animals must have blood with a high colloid osmotic pressure. It would be extremely interesting from this point of view to determine the colloid osmotic pressure of the blood of the giraffe, the only form having its heart at an appreciably greater height above the ground than man. I would expect giraffe blood to have a distinctly higher colloid osmotic pressure than human blood.

In aquatic animals like whales the hydrostatic pressure of the blood at every point is counterbalanced by the pressure of the water acting from the outside, and I would expect therefore that even the blood of large whales will be found to have a low colloid osmotic pressure.

I readily admit that these are loose speculations. Still they have a certain value. Some day they will be put to the test. It will be gratifying, of course, if they turn out to be correct; but their real usefulness will come to light if they turn out to be wrong. In that case they serve as warning guides to show where the reasoning was faulty and to bring it back into proper channels.

The normal blood pressure in the large majority of capillaries in the body (liver and intestine excepted) is undoubtedly lower than the effective osmotic pressure of the blood, and the well known fact that saline solutions introduced into the tissue spaces are normally absorbed into the blood is in good agreement with the theory. In a number of special cases, however, fluid is not absorbed into the blood but is given off rapidly from the blood; and in several such cases, which can be brought about experimentally, we can show that the permeability of the capillary endothelium is definitely increased. A striking instance of this kind is furnished by the action of urethane on the capillaries of the mucous membrane of the frog's tongue.

When a small drop of urethane is placed on the tongue, the capillaries will begin to dilate, much less blood flowing out into the veins than the quantity entering from the arterioles. When the dilatation has reached a certain stage, the red corpuscles become massed together producing stasis, while the plasma disappears, evidently by passing out through the capillary wall. The plasma disappears so rapidly that I thought at first that probably openings were formed between the endo-

thelial cells; but special experiments showed that a suspension of India ink particles having an average size of about 0.2μ (200$\mu\mu$) was retained quantitatively in such capillaries. There are no holes of this order of magnitude in the dilated capillaries, but the permeability is increased so that larger molecules or colloidal particles become able to pass out. If instead of India ink we add soluble starch the molecules of which are supposed to be about 5$\mu\mu$ in size we find that these molecules, which are held back in normal capillaries, pass out readily through those dilated by means of urethane.

We find that dilatation of capillaries, which we can bring about in many different ways and even in some cases by stimulation of nerves, is always accompanied by an increase in permeability, and it seems natural to assume that the stretching and thinning of the endothelial cells is mechanically responsible for their becoming more permeable. This means that the increase in permeability is a normal consequence of dilatation and that we must have every gradation in permeability from the impermeability to all colloids, possessed by contracted capillary walls, through permeability to colloidal particles of very small size up to the permeability to starch possessed by the walls of strongly dilated capillaries.

We possess a certain amount of evidence of the existence of such regular gradations in permeability, but the subject will require a great deal of probably very difficult experimentation.

Though still imperfect and provisional, the information obtained about capillary permeability and its variations can be applied with a certain measure of success to several physiologic and pathologic problems; as, for instance, the mechanism of the "negative pressure" in the thorax, the absorption of substances in the small intestine, the pathologic mechanism of circulatory shock and edema. Time will permit only a very brief discussion of the edema problem.

In discussing edema we must realize to start with that there are several kinds of edema which are theoretically at least quite different, and of which one kind certainly has nothing to do with the state of the capillaries or the capillary circulation. This kind is represented by the cases of intracellular edema sometimes encountered. An instructive example was described recently in a German paper. The cutaneous and subcutaneous tissues of the patient had developed an abnormal affinity for sodium chloride and would take up this substance from the blood when present in normal amount. Along with the sodium chloride the

cells took up, of course, the amount of water necessary to keep the salt in solution. The heart and kidneys were normal, and it is evident that when the capillary wall is freely permeable to both sodium chloride and water the capillaries could neither accelerate nor hinder the development of the edema, which proved easily amenable to treatment by a sodium chloride free diet.

The types of edema which may depend wholly or partly on the capillaries are represented by cases of intercellular edema in which we have free fluid outside the capillaries in tissue spaces and lymph vessels. We must always bear in mind, however, that such cases of edema may be brought about by a combination of factors which it is often impossible to unravel. The capillary blood pressure, the colloid osmotic pressure of the blood, the permeability of the capillary wall, the rate of the lymph flow and the activity of the tissue cells may all play their part in the development and in the disappearance of an edema.

Supposing the capillary wall to remain normal and the tissue cells to be indifferent, we can obtain what I shall call simple "filtration edema" when the intracapillary blood pressure becomes higher than the colloid osmotic pressure of the blood. This is what happens in the feet of a person standing upright without making any movements as a result of the high venous and capillary pressure, and the gradual swelling can easily be followed by measurements.

In an interesting series of experiments a German author, Mende, put a cuff on one arm of subjects and measured the volume of the arm. At a pressure of 630 mm. of water in the cuff he observed an immediate increase in volume, due, of course, to the filling up of veins; but thereupon there was a slow gradual increase, lasting 22 hours in one experiment. Reduction of the pressure to 0 brought about an immediate decrease in volume corresponding to the initial increase followed by a comparatively slow absorption of the edema. Mende found that a pressure of 500 mm. in the cuff would bring about only the initial increase, while no edema was formed. Unfortunately, the venous pressure brought about by a cuff is always lower than the pressure in the cuff and the difference is inconstant, so that we cannot deduce the effective colloid osmotic pressure of the blood in Mende's experiments with any accuracy; but it is, certainly, not very far from the value of 450 mm., which we have found by osmotic determinations.

In cases of filtration edema, the fluid is practically protein-free, with a very low colloid osmotic pressure. Such a fluid has been found in several cases of ascites reported in literature on pathologic conditions and probably brought about by an abnormal increase in the capillary blood pressure in the intestine, where even the normal capillary pressure must be a great deal higher than elsewhere in the body.

An interesting case of general edema in nephrosis has just been studied in my laboratory. The blood pressure in the skin capillaries was higher than normal, amounting to about 150 mm., but the colloid osmotic pressure of the blood was as low as 100 mm. with a protein content of 5%. Twenty mm. is an extremely low osmotic activity for 1% protein, and the explanation was found by an osmotic study of the urine which contained 2.8% protein with an osmotic pressure of 240 mm., or 85 mm. for each %. In this case, therefore, the edema is due to the loss of osmotically active protein in the urine.

In a large number of cases of edema the permeability of the capillary wall is increased, and the edema fluid contains protein. All inflammation edema is of this type, and the fluid in all kinds of blisters usually contains a high proportion of protein. In many, and perhaps in all, cases of this group, dilatation of capillaries due to stimuli of various kinds is the primary cause of the edema.

When an edema fluid contains protein, a direct reabsorption into the capillaries cannot take place. If the capillaries come back to normal, they become impermeable to the protein which has passed out through their walls. There appears, according to our present knowledge, to be two ways in which such fluids can become absorbed. One is the draining off through the lymphatic system, while in the other, which has been studied by Landsberg, the tissue cells give off enzymes which split the proteins into crystalloid molecules, thus making possible a direct absorption into the blood.

I venture to believe that by continued research in the physiology of the capillaries and the osmotic properties of blood and tissue fluids it will eventually become possible to obtain definite information regarding the pathology of edema.

THE EXPLANATION OF THE COLLOIDAL BEHAVIOR OF PROTEINS

JACQUES LOEB

The Rockefeller Institute for Medical Research, New York
Pasteur Lecture, November 24, 1922.

I.

This year's Pasteur lecture coincides with the commemoration of the hundredth anniversary of Pasteur's birth. The application of Pasteur's ideas and discoveries has benefited humanity to such an extent that they have become part of the consciousness of civilized mankind. What is, perhaps, less widely understood is the fact that Pasteur changed the method of medical research. In the study of infectious diseases Pasteur substituted for the method of hit or miss (with the chances infinitely in favor of missing) the method of a definitely oriented search which never fails to give results when properly applied. Thousands of physicians had studied infectious diseases before Pasteur, but they tried to solve their problem by starting from observations of the symptoms of some special disease. This led to no result for the simple reason that without knowing beforehand for what to look—or in other words, without knowing the general cause of infectious diseases—it was impossible to discover the cause of any special infectious process. Pasteur reversed this method by his discovery of the action and omnipresence of micro-organisms, leaving it to the medical men to look for the special agency in the individual cases.

There is little doubt that the old empiricism, still in vogue in some other fields of medicine and in the physiologic sciences, must be replaced by the more rationalistic method of Pasteur of knowing the general fundamental principles before attempting to explain the more special phenomena, since, unless we follow this method, we never know which of the details we observe are significant and which are negligible.

II.

Living matter is essentially colloidal in character, and we cannot well conceive of an organism consisting exclusively of crystalloidal matter. This fact suggests that life phenomena depend on or are intrinsically linked with certain characteristics of colloidal behavior.

It is, therefore, natural that a systematic study of the nature of special life phenomena should be preceded by a scientific theory of colloidal behavior. By a scientific theory, however, we do not understand speculations or guesses built on qualitative experiments or no experiments at all, but the derivation of the results from a rationalistic, mathematical formula which permits us to calculate, with an adequate degree of accuracy, the quantitative measurements of colloidal behavior.

Proteins are amphoteric electrolytes which are capable of forming salts with either alkalies or acids. With alkalies they form salts like Na proteinate, Ca proteinate, etc., and with acids they form salts like protein chloride, protein sulphate, etc. Whether they do the one or the other depends on the hydrogen-ion concentration of the protein solution. There is one definite hydrogen-ion concentration at which a protein can combine practically with neither acid nor alkali, and this hydrogen-ion concentration, which may be different for different proteins, is called the iso-electric point. The iso-electric point is (in terms of Sørensen's logarithmic symbol) for gelatin and casein at P_H 4.7; for crystalline egg albumin at P_H 4.8. Gelatin can combine with acid only or practically only when the P_H is less than 4.7 and with alkali only or practically only when the P_H is higher than 4.7; or, in other words, when a salt, for example, $NiCl_2$, is added to gelatin solutions of different P_H Ni gelatinate can be formed only when the P_H is greater than 4.7; and when $K_4Fe(CN)_6$ is added, gelatin-$Fe(CN)_6$ can be formed only when the P_H is less than 4.7. This can be shown by methods discussed in a recent book.[1]

The proof that proteins combine stoichiometrically with acids and alkalies can be furnished by titration curves. For this purpose (and perhaps for work with proteins in general) it is necessary to use as standard material protein of the P_H of the iso-electric point. We have seen that proteins combine with acids only at a P_H below that of the iso-electric point, which for gelatin or casein is about P_H 4.7 and for crystalline egg albumin 4.8. It happens that at a P_H below 4.7 most of the weak dibasic and tribasic acids dissociate as monobasic acids. Thus H_3PO_4 dissociates into H^+ and the monovalent anion $H_2PO_4^-$. Hence, if acids combine stoichiometrically with iso-electric protein, it should require exactly three times as many cc of 0.1 N H_3PO_4 to bring a 1% solution of an iso-electric protein, e. g., gelatin or crystalline egg

[1] Loeb, J.: Proteins and the Theory of Colloidal Behavior, New York and London, 1922

albumin or casein, to the same hydrogen-ion concentration, e. g., P_H 3.0, as it requires of 0.1 N HCl or HNO_3. Titration experiments show that this is the case. Further, since H_2SO_4 is a strong acid, splitting off both H-ions even at a P_H below 4.7, the same number of c c of 0.1 N H_2SO_4 as of HCl should be required to bring 1 gm. of iso-electric protein in 100 c c of solution to the same P_H, e. g., 3.0; and this also was found to be true.

Chart 1 gives the titration curves for crystalline egg albumin for 4 acids, HCl, H_2SO_4, H_3PO_4, and oxalic acid. One gram of iso-electric albumin was in 100 c c H_2O containing various c c of 0.1 N acid. These

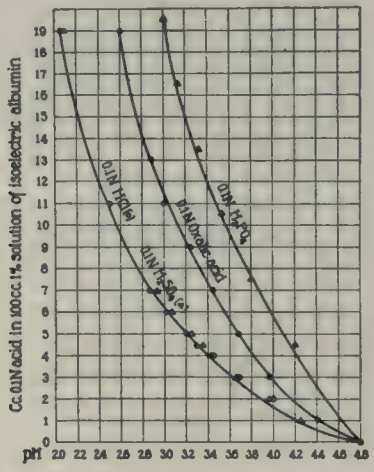

Chart 1.—Titration curves for crystalline egg albumin for HCl, H_2SO_4, H_3PO_4 and oxalic acid.

c c of 0.1 N acid in 100 c c solution are the ordinates of the curves in Chart 1. The abscissae are the P_H to which the protein solution was brought by the addition of acid. It takes always exactly three times as many c c of 0.1 N H_3PO_4 as it takes c c of 0.1 N HCl or H_2SO_4 to bring 1 gm. of iso-electric albumin in 100 c c solution to the same P_H. In order to bring the 1% solution of originally iso-electric albumin to P_H 3.2, 5 c c of 0.1 N HCl or H_2SO_4 and 15 c c of 0.1 N H_3PO_4 must be contained in 100 c c of the solution. To bring the albumin to P_H 3.4, 4 c c of 0.1 N HCl or H_2SO_4 and 12 cc of 0.1 N H_3PO_4 must be contained in the solution, and so on.

Oxalic acid is, according to Hildebrand, a monobasic acid at a P_H of 3.0 or below, but begins to split off the second hydrogen-ion in increasing proportion above P_H 3.0. The titration curves show that about twice as many c c of 0.1 N oxalic acid as 0.1 N HCl are required to bring the 1% solution of iso-electric albumin to the same P_H below 3.0, whilte it takes less than twice as many c c of 0.1 N oxalic acid as 0.1 N HCl to bring the albumin solution to the same P_H if the P_H is above 3.0.

It can be shown in the same way with the aid of titration curves that iso-electric albumin combines with alkalis in the same stoichiometrical way as any acid; e. g., acetic acid, would combine with the same alkalies. If the c c of 0.1 N KOH, NaOH, $Ca(OH)_2$, or $Ba(OH)_2$ in 100 c c solution required to bring a 1% solution of iso-electric protein to the same P_H are plotted as ordinates over the P_H of the protein solution as abscissae, it is found that the values for all 4 alkalis fall on one curve, as they should if the combination occurred strictly stoichiometrically.

The same stoichiometrical results were obtained also with casein and gelatin by the writer, and with edestin and serum globulin by Hitchcock. There is little doubt that they will be obtained in the case of all proteins. It follows from this that proteins react with acids and alkalis in the same way as do amphoteric crystalloids like amino-acids. If the methods for measuring the hydrogen-ion concentration of protein solutions had been employed by the colloid chemists, nobody would have thought of suggesting that proteins react with acids and alkalis according to the empirical adsorption formula of Freundlich instead of stoichiometrically.

The purely chemical character of the combination of proteins with hydrochloric acid can also be demonstrated by measuring the chlorine-ion concentration of the solutions of protein chloride. When HCl is added to NH_3 (according to Werner) the H-ions of the HCl are attracted to the nitrogen of the ammonia, while the Cl-ions remain unaltered. The same type of reaction occurs when HCl is added to a solution of iso-electric gelatin. This was proven by measurements of the P_{Cl} of solutions of gelatin chloride. Different c c of 0.1 N HCl were contained in 100 c c of 1% solutions of originally iso-electric gelatin and the P_H and P_{Cl} of the solutions were measured, the P_H with the hydrogen electrode and the P_{Cl} with the calomel electrode. It was found that

the P_{Cl} was the same as if no gelatin had been present, while the P_H was, of course, higher; thus showing that part of the hydrogen combines with the NH_2 and NH groups of the protein molecule, while the Cl remains free (table 1). Dr. Hitchcock has obtained similar results with crystalline egg albumin, edestin, casein, and serum globulin, by using a silver chloride electrode, so that it is possible to state that these results are true for most if not all proteins.

TABLE 1.—CHLORINE POTENTIALS IN PRESENCE AND ABSENCE OF PROTEIN

Cubic Centimeters of 0.1 N HCl in 100 c c Solution	Solution Containing No Gelatin		Solution Containing 1 Gm. of Iso-Electric Gelatin in 100	
	P_H	P_{Cl}	P_H	P_{Cl}
2	2.72	2.72	4.2	2.68
3	2.52	2.54	4.0	2.53
4	2.41	2.39	....	....
5	2.31	2.29	3.60	2.33
6	2.24	2.26	3.41	2.25
7	2.16	2.18	3.23	2.18
8	2.11	2.12	3.07	2.11
10	2.01	2.01	2.78	2.025
15	1.85	1.85	2.30	1.845
20	1.72	1.76	2.06	1.76
30	1.55	1.59	1.78	1.60
40	1.43	1.47	1.61	1.47

The titration curves prove another fact, namely, that the salts of proteins are strongly hydrolyzed. When we add acid, e. g. HCl, to iso-electric protein, part of the acid combines with the protein giving rise to protein chloride, while the rest of the acid remains free. There is, then, an equilibrium between free HCl, protein chloride, and non-ionogenic (or iso-electric) protein. The more acid is added to originally iso-electric protein, the more protein chloride is formed, until finally all the protein exists in the form of protein chloride. It is possible to find out from the P_H measurements how much of the acid added is free, and by deducting this value we know how much is in combination with the protein. By saturating the protein with acid, the combining weight of a protein with acid can be found. Hitchcock found in this way that the combining weight of gelatin is about 1090.

III.

The colloidal behavior of proteins shows itself in a peculiar effect of electrolytes—acids, alkalis, or salts—on such properties as the swelling of gels or the osmotic pressure or viscosity of protein solutions. All these properties—swelling, osmotic pressure and viscosity—are

affected by electrolytes in an almost similar way; suggesting that all are due to the same cause. We shall see that by giving the explanation for one of these properties, osmotic pressure, we shall by implication give the explanation for all of them.

Measurements of the osmotic pressure of solutions of a protein —gelatin, crystalline egg albumin, casein, and edestin—were made with solutions containing 1 gm. dry weight of originally iso-electric protein in 100 c c of solution; and the 100 c c of solution included also varying concentrations of 0.1 N acid. These solutions were put into collodion bags suspended in water free from protein. The outside water was

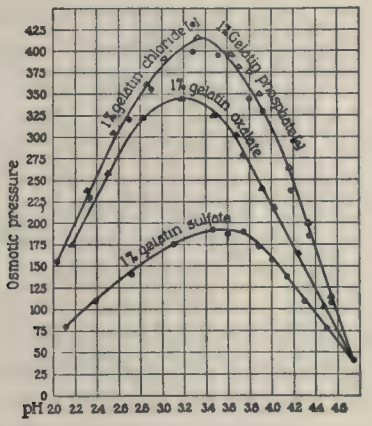

Chart 2.—Variation of osmotic pressure with the P_H of protein solution and the valency of the anion of the acid used.

at the beginning of the experiment brought to the same P_H as that of the protein solution, using always the same acid as that added to the protein. The measurements of the osmotic pressure were read after 18 hours, when osmotic equilibrium was established. It was found that the osmotic pressure varied in a characteristic way with the P_H of the protein solution and the valency of the anion of the acid used. This effect is shown in the curves in Chart 2 which were obtained from gelatin solutions. But the curves are similar in the case of other proteins, such as crystalline egg albumin, casein, or edestin. These curves show that the osmotic pressure of a protein solution is a minimum at the iso-electric point, that it increases when little acid is added until a maximum is reached, and that on the further addition of acid the

osmotic pressure is again diminished. They show, moreover, that only the valency and not the nature of the anion of the acid influences the osmotic pressure of a protein solution. We know from the titration curves that in the case of H_3PO_4 the anion in combination with the protein is not the trivalent PO_4 but the monovalent H_2PO_4; and the curves in Chart 2 show that the influence of phosphoric acid and hydrochloric acid on the osmotic pressure is the same if measured for the same P_H of the protein solution. Oxalic acid is a monobasic acid below P_H 3.0, and we notice that the descending branch of the oxalic acid curve below P_H 3.0 practically coincides with the descending branch of the HCl curve. The curve for the influence of H_2SO_4 is only about half as high as that for HCl, and we know from the titration curves that the anion of protein sulphate is bivalent. It was found that all monobasic acids, e. g., HBr, HNO_3, acetic acid, etc., and all weak dibasic or tribasic acids, e. g., tartaric, malic, citric, etc., which below P_H 4.7 dissociate as monobasic acids, give osmotic pressure curves identical with those for HCl and H_3PO_4. We may, therefore, draw the conclusion that only the valency but not the nature of the acid influences the osmotic pressure of protein solutions, that all acids which are monobasic on the acid side of the iso-electric point of a protein influence its osmotic pressure in the same way, and that this influence is considerably greater than the influence of strong dibasic acids like H_2SO_4.

If alkali is added to a solution of iso-electric protein, it can be shown that the addition of a little alkali increases the osmotic pressure until a maximum is reached, when the addition of more alkali depresses the osmotic pressure again. All alkalis with monobasic cation like Li, Na, K, NH_4, have the same effect at the same P_H, while alkalis and all dibasis cations like Ca or Ba act alike, the curve for the effect of the alkalis with divalent cation being only about half as high as that of the alkalis with monovalent cation.

A third fact (discovered by R. S. Lillie) is that the addition of salts to a solution of a protein salt always depresses the osmotic pressure.

The curves representing the influence of acids and salts on the osmotic pressure are almost identical or very similar to those representing the influence of the same acids and salts on swelling and viscosity. These results are specific for colloidal behavior, and any theory of colloidal behavior will have to give not only a qualitative but a quantitative theory of these curves.

It was suggested by Zsigmondy that the influence of acid on osmotic pressure was due to an influence on the degree of dispersion of the protein in solution, but since the degree of dispersion cannot be accurately measured, this suggestion is only a qualitative speculation. But it is of no use even as a qualitative speculation, since it fails to account for the fact that viscosity and swelling are affected in a similar way as osmotic pressure. The correct explanation is as follows. When acid (or alkali) is added to a solution of an iso-electric protein, part or all of this is transformed into an ionizable protein salt, according to the amount of acid added. This ionization of the protein causes the colloidal behavior, on account of the inability of protein ions to diffuse through membranes which are easily permeable to crystalloidal ions, such as collodion or parchment membranes or the walls of capillaries or probably of all cells. Now it was shown by Donnan that whenever the diffusion of one type of ions such as colloidal ions is prevented by a membrane which is readily permeable to crystalloidal ions, an unequal distribution of the diffusible crystalloidal ions results on the opposite sides of the membrane. This unequal distribution of diffusible crystalloidal ions is the cause of the colloidal behavior of proteins.

IV.

When a collodion bag is filled with a solution of gelatin chloride of P_H 3.0 and the bag is immersed in an acqueous solution of HCl also of P_H 3.0 but free from protein, acid is driven from the protein solution into the outside aqueous solution free from protein. Donnan has shown thermodynamically that when osmotic equilibrium is established the products of the concentrations of each pair of oppositely charged diffusable ions (e. g., H and Cl in the case of gelatin chloride) are equal on the opposite sides of the membrane. Let x be the molar concentration of the H and Cl ions on the outside, y the molar concentration of the free H and Cl ions inside the protein solution, and z the concentration of the Cl ions in combination with the protein; then equilibrium is defined by the following equation, first used by Procter and Wilson to explain the influence of acid on swelling,

$$x^2 = y(y + z) \qquad (1)$$

The first step in an attempt to explain the influence of acids, alkalis, and salts on the osmotic pressure of protein solutions is to find out whether the variations in osmotic pressure under the influence of acids

as shown in Chart 2 are accompanied by corresponding differences in the concentration of diffusible ions inside and outside the protein solution, and whether these differences can be calculated from Donnan's equilibrium equation (1).

The writer was able to show that this is true by making measurements of a property of protein solutions, which had received little if any attention in colloid chemistry, namely, the measurements of the membrane potentials existing between a protein solution and the surrounding aqueous solution at the time of osmotic equilibrium.

Donnan's equilibrium formula can be written in the form $\frac{x}{y} = \frac{y+z}{x}$ where $\frac{x}{y}$ is the ratio of the molar concentration of the hydrogen-ions outside to the concentration of the hydrogen-ions inside, while $\frac{y+z}{x}$ is the ratio of the molar concentration of the chlorine ions inside to that outside. Donnan had shown that there should exist a potential difference between the inside and outside solutions, which at 24 C. should be equal to $59 \times \log \frac{x}{y}$ millivolts or $59 \times \log \frac{y+z}{x}$ millivolts. Since P_H inside is $= -\log y$, and P_H outside is $= -\log x$, $\log \frac{x}{y}$ is equal to P_H inside minus P_H outside. P_H inside and P_H outside can be determined directly with the aid of the hydrogen electrode; $\log \frac{y+z}{x}$ is equal to P_{Cl} outside minus P_{Cl} inside, and this quantity can be measured directly by titration or with the silver chloride electrode.

On the other hand, the P.D. between the protein solution and the surrounding aqueous solution across a collodion membrane can be measured directly with the aid of a Compton electrometer and a pair of identical indifferent calomel electrodes (and saturated KCl). If the unequal distribution of diffusible crystalloidal ions (e. g., H and Cl in the case of gelatin chloride) on the opposite sides of the membrane is really determined by the Donnan equilibrium, then the P.D. observed directly with the pair of identical calomel electrodes should be equal to the P.D. calculated in millivolts from the values $59 \times$ (P_H inside minus P_H outside) or from $59 \times$ (P_{Cl} outside minus P_{Cl} inside), where P_{Cl} or P_H may be obtained by titration or by the silver chloride or hydrogen electrodes, respectively. The writer has made these measurements and found that when various quantities of acid are added to solutions of iso-electric protein—e. g., crystalline egg albumin, or gelatin, or casein—the observed membrane potentials always agree with the membrane potentials calculated on the basis of Donnan's equation within 1 or 2 millivolts, i. e., within the limits of accuracy of the measurements.

The net results of extensive measurements of membrane potentials was, first, that when a protein solution, enclosed in a collodion bag (impermeable to protein ions but permeable to crystalloidal ions), is in osmotic equilibrium with an outside aqueous solution, the concentrations of crystalloidal ions in the protein solution and in the outside aqueous solution are not the same; and second, that the difference in the two concentrations can be calculated from Donnan's equilibrium equation.

V.

We are now in a position to explain the osmotic pressure curves in Chart 2. The colloid chemists would have taken it for granted that such curves were due to an influence of the acids on the state of dispersion or on some other real or imaginary colloidal property of proteins. Before we have a right to indulge in such speculations we must realize that these curves of observed osmotic pressure are not exclusively the expression of the osmotic pressure due to the protein particles, or protein molecules, and protein ions alone, but are also the result of the demonstrable unequal concentrations of the crystalloidal ions on the opposite sides of the membrane, caused by the establishment of a Donnan equilibrium. In other words, the observed osmotic pressure of a protein solution needs a correction due to the Donnan equilibrium before we can begin to speculate on the cause of the influence of acid on these curves, and it is our purpose to calculate the value of this correction.

We begin with the curve expressing the influence of HCl on the osmotic pressure of a 1% solution of originally iso-electric gelatin, and we consider the distribution of ions inside the protein solution and in the aqueous solution outside the collodion bag containing the protein solution at osmotic equilibrium. We also assume complete electrolytic dissociation of gelatin chloride as well as HCl. Let a be the molar concentration of the protein molecules and ions, let z be the molar concentration of the Cl ions in combination with the ionized protein, let y be the molar concentration of the hydrogen-ions of the free HCl inside the protein solution; the molar concentration of the Cl ions of this HCl is also y. In that case the osmotic pressure of the protein solution is determined by $a + 2y + z$. From this must be deducted the osmotic pressure of the HCl of the outside aqueous solution. If x is the molar concentration of the H-ions of the outside solution, it is also the molar concentration of the Cl ions. Hence the observed osmotic pressure of a protein solution is determined by the

molar concentration: $a + 2y + z - 2x$. Chart 2 shows how this value varies with the P_H of the protein solution (i. e., y). In order to arrive at a theory concerning the influence of HCl on the osmotic pressure of protein solutions it is necessary to calculate the value of $2y + z - 2x$ and to deduct it from the observed osmotic pressure of the protein solution. The term $2y + z - 2x$ we will call the Donnan correction. In this term y and x can be calculated from the measurements of the P_H, P_H inside being $-\log y$ and P_H outside being $-\log x$; z can be calculated from x and y with the aid of the Donnan equation (1) $\epsilon = \frac{(x+y)(x-y)}{y}$ since we now know that x and y are determined by the Donnan equilibrium. If the value of $2y + z - 2x$ is calculated for different P_H of a gelatin chloride solution (of the same concentration of originally iso-electric gelatin which in this case was 1%); and if from this value is calculated the osmotic pressure due to this excess of the molar concentration of crystalloidal ions inside the protein solution over that outside, it is found that the curve for the Donnan correction is almost identical with the curve for the observed osmotic pressure. In other words, it turns out that the increase in osmotic pressure of a 1% solution of originally iso-electric gelatin on the addition of little acid until a maximum is reached, and the diminution of osmotic pressure on the addition of further acid are not due to any variation in the state of dispersion of the protein, or any other real or imaginary "colloidal" property of the protein, but purely to the fact that protein ions cannot diffuse through the collodion membrane, which is easily permeable to crystalloidal ions; as a consequence of which the molar concentration of the crystalloidal ions must always be greater inside the protein solution than outside. What varies with the P_H of the gelatin solution is the quantity of the excess of $2y + z$ over $2x$. This follows from the Donnan equation (1) according to which $x = \sqrt{y^2 + yz}$ or $2x = \sqrt{4y^2 + 4yz}$ while $2y + z = \sqrt{4y^2 + 4yz + z^2}$. Now it is obvious that $\sqrt{4y^2 + 4yz + z^2} > \sqrt{4y^2 + 4yz}$, i. e., the concentration of the crystalloidal ions inside the protein solution $2y + z$ is always greater than the concentration of the crystalloidal ions $2x$ outside, when z is not 0 or 00.

If we substitute for the term $2y + z - 2x$ of the Donnan correction the identical term $\sqrt{4y^2 + 4yz + z^2} - \sqrt{4y^2 + 4yz}$ we can visualize why the osmotic pressure is a minimum at the iso-electric point, why it increases with the addition of little acid, reaching a maximum, and why it diminishes again with the addition of more acid.

At the iso-electric point no protein is ionized, and z being zero, the whole term $\sqrt{4y^2 + 4yz + z^2} - \sqrt{4y^2 + 4yz}$ becomes zero. Hence, at the iso-electric point the observed osmotic pressure is purely that due to the protein, which is very low on account of the high molecular weight of gelatin.

When little acid, e. g., HCl, is added to the solution of iso-electric gelatin, gelatin chloride is formed and some free acid remains, due to hydrolytic dissociation. Hence both z (the concentration of Cl ions in combination with protein) and y (the Cl ions of the free HCl existing through hydrolysis) increase, but z increases at first more rapidly than y, and hence the excess of concentration of ions inside over that of ions outside increases until the greater part of protein is transformed into protein chloride, when the excess of crystalloidal ions inside over those outside reaches a maximum. From then on z increases comparatively little, while y increases considerably with further addition of acid, so that z becomes negligible in comparison with y. This explains why the Donnan correction becomes zero again when enough acid is added, and why the observed osmotic pressure becomes as low again as at the iso-electric point.

In the same way it can be shown why the addition of salt has only a depressing effect on the osmotic pressure. Let us assume that there is inside the bag a gelatin chloride solution of P_H 3.0 to which NaCl is added. z (the concentration of Cl ions in combination with the gelatin) will not increase with the addition of salt, while y (the concentration of the Cl ions *not* in combination with gelatin) will increase. Hence with the increase in the concentration of the salt the value of $\sqrt{4y^2 + 4yz + z^2} - \sqrt{4y^2 + 4yz}$ will become smaller, finally approaching zero.

When another salt than a chloride, e. g., $NaNO_3$, is added to a solution of gelatin chloride, we may assume that the gelatin in solution is gelatin nitrate.

Chart 3 gives a comparison of the curves for the observed osmotic pressure and for the Donnan correction. Both curves rise in a parallel way from the iso-electric point, reaching a maximum which is 450 mm. H_2O pressure in the case of the observed osmotic pressure and slightly lower in the case of the Donnan correction. The observed osmotic pressure should be higher than the Donnan correction by the osmotic pressure due to the protein solution itself. A difference exists in the values between P_H 4.6 and 3.2 but disappears later, and this difference is in all probability the expression of value a, i. e., the osmotic

pressure due to the protein itself. The disappearance of this difference at P_H below 3.2 is probably due to the fact that an error of one unit in the second decimal of the P_H causes a considerable error in the calculations of z, which increases when the P_H is too low.

Chart 3 shows that when we correct the observed osmotic pressure for the Donnan effect it follows that the influence of the P_H of the acid on the osmotic pressure is entirely or practically entirely due to the excess of the concentration of crystalloidal ions inside the membrane over that outside, and that this excess is caused by the Donnan equilibrium. The osmotic pressure of the protein itself is either not altered by

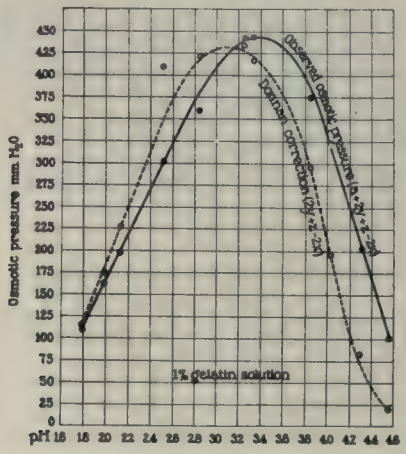

Chart 3.—Curves for observed osmotic pressure and for the Donnan correction.

the addition of acid, or, if it is altered, the effect is too small to be noticeable. There is, then, nothing left for the "dispersion theory" or for any other of the colloidal speculations to explain. These results were confirmed for crystalline egg albumin and casein by the writer, and for edestin by Hitchcock. We now understand why only the valency and not the nature of the ion plays a rôle in the osmotic pressure of protein solutions. The equilibrium equation is one of the second degree when the ion with which the protein is in combination is monovalent, while it is of the third degree when the ion is divalent. Only the valency of the ion and not its nature enters into the Donnan equation.

We can therefore summarize these results by stating that the so-called colloidal behavior of protein solutions, as far as osmotic pressure is concerned, is merely the result of an equilibrium condition of classical chemistry which results in an excess of the concentration of crystalloidal ions inside the protein solution over that of an outside aqueous solution, when the two solutions are separated by a membrane which is permeable to crystalloidal ions but impermeable to protein ions. The colloidal behavior of proteins depends therefore entirely on the relative nondiffusibility of protein ions through membranes which are easily permeable to crystalloidal ions. Since the majority of membranes in plants and animals belong to this class, it can easily be surmised how great a rôle the proteins must play in the regulation of osmotic pressure in the body.

VI.

It remains to show briefly why swelling and viscosity of protein solutions are affected in a similar way by electrolytes as is the osmotic pressure. The answer is that we are dealing in both cases with the same fundamental property, namely, osmotic pressure.

In 1910, Procter made the ingenious suggestion that the swelling of gelatin might be an osmotic phenomenon, and in subsequent papers he and J. A. Wilson put this theory on a quantitative basis by deriving it from the Donnan equilibrium. They showed that the swelling of a solid gel of gelatin in hydrochloric acid can be explained quantitatively on the basis of the Donnan equilibrium on the assumption that there exists an excess of concentration of crystalloidal ions inside (in this case H and Cl) over the concentration of the same ions outside, and that the excess of osmotic pressure inside the gel over that outside due to this Donnan effect accounts for that share of the swelling which is caused by the influence of the acid. The agreement of their calculated values with the observed values is excellent. The writer is inclined to consider Procter's theory of swelling and the proof of this theory by Procter and J. A. Wilson as the most brilliant contribution to the theory of colloidal behavior next in importance only to Donnan's theory of membrane equilibria. There was only one detail left by these authors, namely, to prove the existence of membrane potentials between the gel and the surrounding aqueous solution at equilibrium. The writer was able to fill this gap and to show that the observed P.D. between gel and

surrounding aqueous solution can be calculated with a fair degree of accuracy from the value P_H inside minus P_H outside with the aid of Nernst's logarithmic formula.

VII.

It may seem strange that the influence of electrolytes on the viscosity of certain protein solutions should be explained in the same way, but this seems to be the case. According to Einstein's formula, the viscosity of an aqueous protein solution is a linear function of the relative volume of the solute occupied in the solution, as expressed in the formula $\eta = \eta_0 (1 + 2.5 \phi)$ where η is the viscosity of the solution, η_0 that of pure water, and ϕ the proportion of the volume of the solute to that of the solution. If, therefore, the addition of little acid to a 1% solution of iso-electric gelatin increases the viscosity of the solution until a maximum is reached, and if the addition of more acid depresses the viscosity again, it follows that the addition of acid changes the relative volume occupied by the gelatin in water. This is only possible by water being absorbed by the protein, and the question is how to account for this absorption of water by the protein under the influence of acid. Pauli assumed that the ionized protein surrounds itself with a jacket of water which is lacking in the nonionized protein. If this were true, all the proteins and amino-acids should show such an influence of acid on the viscosity of their solutions. The writer found that no such influence exists in the case of amino-acids and at least one protein, namely, crystalline egg albumin; if Pauli's assumption were correct, there is no reason why crystalline egg albumin should not show the same influence of acid on viscosity which is found in the case of gelatin. The difference between gelatin and crystalline egg albumin is that the former sets to a solid gel if the temperature is not too high, while the latter does not. The formation of a continuous gel in the gelatin solution is preceded by the formation of submicroscopic aggregates which occlude water and which are capable of swelling, and these aggregates or precursors of the continuous gel increase in size and number on standing. To test this idea the writer made experiments with suspensions of powdered gelatin in water and found that such suspensions of powdered gelatin had a much higher viscosity than a freshly prepared solution of gelatin. This was to be expected if the influence of acid on the viscosity of proteins is due to the swelling of submicroscopic particles of gel. It harmonizes with this fact that the viscosity of solutions of crystalline egg albumin is of a low order of

magnitude, which was to be expected if solutions of crystalline egg albumin contain few or no miscellæ. It was found, moreover, that the viscosity of suspensions of powdered gelatin increased under the influence of acid or alkali in the same way as did the swelling of jellies or the osmotic pressure of protein solutions. The viscosities were measured at 20 C. When the suspension of powdered gelatin was melted, it was found on rapid cooling to 20 C. that the viscosity was considerably lower and that the influence of acid had almost disappeared. By these and a number of similar experiments, it was possible to prove that the similarity between the influence of electrolytes on the viscosity of gelatin solution and the influence of electrolytes on osmotic pressure is due to the fact that the influence on viscosity in such cases is in reality an influence on the swelling of submicroscopic protein particles. This proof was made complete by showing that there exists a Donnan equilibrium between powdered particles of gelatin and a surrounding weak gelatin solution.

VIII.

It may not be amiss to illustrate by way of an example why it is that the neglect of measuring the hydrogen-ion concentration of protein solutions necessarily leads into errors. In a paper published in 1921 by Kuhn,[2] it was intended to show that different acids of the same valency have different effects on the swelling of gelatin. In order to furnish such a proof it is necessary to start with iso-electric gelatin and to compare the effect of different acids on the swelling of this iso-electric gelatin at the same hydrogen-ion concentration of the gel, since only in that case have the gels the same concentration of gelatin ions. Instead of starting with iso-electric gelatin or gelatin of a measured P_H, Kuhn failed to measure the P_H of his gelatin, though it makes quite a difference whether acid is added to iso-electric gelatin or to gelatin at another P_H. Further, instead of measuring the P_H of the gel with the hydrogen electrode, Kuhn calculated the hydrogen-ion concentrations from Kohlrausch's tables as if acid had been added to water free from gelatin and as if the presence of the protein did not alter the hydrogen-ion concentration. Our titration curves, however, show that when acid is added to iso-electric gelatin, the hydrogen-ion concentration is less than when acid is added to water free from protein. And finally, on account of the Donnan equilibrium the P_H inside and outside the gel are entirely

[2] Kuhn, A.: Kolloidchem. Beihefte, 1921, 14, 147.

different; yet no mention is made of the Donnan equilibrium in the paper referred to. The hydrogen-ion concentrations of protein solutions which were considered as equal by Kuhn were on account of all these errors entirely different, and it is quite natural that Kuhn came to the conclusion that different monobasic acids have different effects on swelling, since it would have been a miracle if with his faulty methods he had ever compared the effects of two acids at the same P_H. The same criticism applies to all the older experiments on the influence of electrolytes on swelling in which the authors reached the conclusion that different anions of the same valency have different effects on swelling (Hofmeister series). In all these experiments the authors failed to measure the P_H of their gels and erroneously attributed effects due to differences of the P_H of the gels to the difference in the nature of the anion.

IX.

We therefore come to the conclusion that the chemistry of proteins does not differ from the chemistry of crystalloids, and that proteins combine stoichiometrically with acids and alkalies forming protein salts which dissociate electrolytically. The enormously large protein ions and molecules cannot diffuse freely through gels or many membranes which are easily permeable to small crystalloidal ions. This fact leads, under proper conditions, to an unequal distribution of the diffusible crystalloidal ions between a protein solution and an outside aqueous solution; or between a protein gel and an aqueous solution. In this distribution the total concentration of crystalloidal ions is always greater inside the protein solution or inside a gel than in the surrounding aqueous solution. This is the cause of the colloidal behavior of protein solutions and protein gels. Measurements of membrane potentials have shown that this excess of the concentration of crystalloidal ions inside over the concentration of the crystalloidal ions outside the protein solution or the gel and consequently all the effects of electrolytes on osmotic pressure, swelling, and viscosity of proteins, can be calculated with a satisfactory degree of accuracy from Donnan's equilibrium equation, which is not an empirical but a rationalistic mathematical formula. We can therefore state that it is possible to explain the colloidal behavior of proteins quantitatively on the basis of a rationalistic mathematical formula. What appeared at first as a new chemistry, the so-called colloid chemistry, now seems to have been only an overlooked equilibrium condition of classical

chemistry; at least as far as the proteins are concerned. The oversight was due to two facts: first, to the failure of colloid chemists to measure the hydrogen-ion concentration of their solutions, which happens to be the chief variable in the case, and second, to their neglect of measuring and taking into consideration the membrane potentials of protein solutions and protein gels, which furnish the proof that the theory of membrane equilibria must be used to explain the colloidal behavior of proteins.

FRANK SEWARD JOHNSON

1856-1922

Dr. Frank Seward Johnson was born April 18, 1856, in Chicago. His preliminary education was acquired in a private school, with one year's study in Stuttgart, Germany. He prepared for college in the Chicago Academy and entered Northwestern University in 1874, receiving the degree of A.B. in 1878. Three years later, he was awarded his master's degree by the university, and in the same year he earned his medical degree from Chicago Medical College, the medical department of the university.

A year in Vienna and another as intern at Cook County Hospital preceded his entry in practice in Chicago. From boyhood he had been trained by his father in the use of instruments of precision, especially the microscope, and in chemical work, so that his skill with these means of diagnosis soon brought him into prominence.

In 1883, he was appointed demonstrator of histology in Chicago Medical College and the next year was made professor of that subject. Unfortunately, his work was interrupted by repeated attacks of appendicitis, which forced him to give up teaching for several years. On recovery he became professor of medicine, and later he was made dean of the faculty. About this time the college completed the union with the university and became the Northwestern University Medical School. In 1910, he was elected emeritus dean and professor of medicine.

Dr. Johnson was consulting physician to Michael Reese, Mercy and the Woman's hospitals. He was a member of the American Medical Association, the Institute of Medicine, and other medical societies, the Chicago Academy of Sciences, the Cliff Dwellers and the Chicago Literary and University Clubs. He was also a trustee of the John Crerar Library.

On Sept. 30, 1890, he married Miss Elizabeth Burbank Ayer, daughter of Mr. and Mrs. Edward E. Ayer of Chicago. There are two sons, Hosmer Allen Johnson, a California architect, and Edward Ayer Johnson. In 1917, Dr. and Mrs. Johnson removed to Pasadena, Calif., where, among old friends, they established a new home. He died there, April 22, 1922.

FRANK SEWARD JOHNSON
1856-1922

Dr. Johnson was a man of rare good judgment, with the ability to marshal his facts and to express his ideas and opinions in perfect order and with telling effect. His mind was of the judicial type. He was alert to detect deceit, and quick to resent any compromise with evil and error. He was a profound student, precise, painstaking and accurate.

Dr. Hosmer Allen Johnson (1824-1901), the father of Dr. Frank S. Johnson, was one of the founders of the Chicago Medical College (Northwestern University Medical School) and a teacher in the institution until his death. He was one of the leaders of the medical profession in Chicago and in this country. He was one of the founders of the Association of American Physicians. He was a man of rare culture, a gentleman of the old school, forceful yet gentle, possessed of a scientific mind; he was one of the first physicians of the United States to utilize the microscope, the fever thermometer and other instruments of precision and diagnosis of that day. As a teacher he had the quality of mind which enabled him to impart knowledge clearly and forcefully, and he was recognized by all of his students as a character builder.

His son, Frank Seward Johnson, inherited many of the qualities of mind and heart of his illustrious father and also resembled him physically. The name of both father and son are inseparably linked with the higher development of medical teaching and practice in the Middle West.

THIRD ANNUAL REPORT TO THE GOVERNORS OF THE INSTITUTE OF MEDICINE OF A COMMITTEE APPOINTED TO INQUIRE INTO THE QUESTION OF NECROPSIES IN THE HOSPITALS OF CHICAGO

The response of the hospitals of Chicago to the questionnaire for 1921 shows a growing interest in pathology and in the improvement of clinical work of the hospital staffs. Thirty-eight of the hospitals having a bed capacity of 50 or more responded. The capacity of the reporting hospitals for 1921 was 8,599 beds. There were 157,257 admissions and 7,269 deaths. Permission necropsies were made in 1,206 cases as against 872 in 1920 and 789 in 1919. The increase in two years is somewhat over 50%. In addition to permission necropsies, coroner's necropsies were made in 965 cases, including approximately 675 at the County Hospital; many of these yielded information and material of highest value for teaching, and the improvement of methods in the care of the sick.

A further analysis, omitting the figures for the County Hospital in which notable gains have been made during the year, indicates the trend of interest in the teaching of pathology in the other hospitals of the city. There were 663 permission necropsies in 4,329 deaths (15%) in these hospitals, as against 556 in 1920 and 474 in 1919, an increase of about 40% in two years.

In 1921, eighteen hospitals showed an increase in percentage of necropsies over 1920. In 9 hospitals the percentage of permission necropsies was over 20 (50.0, 49.2, 44.0, 37.5, 36.3, 29.4, 28.5, 26.8, 23.5) as against 6 hospitals having over 20% in 1920.

On the other hand, in 10 hospitals which receive general medical and surgical patients, there were 852 deaths and 21 permission necropsies, a percentage of about 2.5. In 3 of these, according to reports received, there has not been a necropsy in three years. It is believed that thoughtful consideration of these facts by the trustees and staffs of the hospitals must suggest to them that both the hospitals and staffs are missing an important opportunity for improving their professional work and the service rendered to patients.

As has been noted in previous reports, prejudice and ignorance, religious scruples, and in some instances deliberate opposition by

1922	Beds	Patients	Deaths	Necropsies		Percentage Permission			Pathologist
				Permission	Coroner	1921	1920	1919	
Alexian Brothers	285	No report	No report	No report	No report	No report	7.4	4.9	Brother Surgius
American	160	4,441	49	4	2	8.1	2.9	12.1	H. Rosenberg
Durand	60	841	43	19	0	44.0	37.1	24.4	L. Hektoen
Augustana	260	3,884	211	19	10	9.0	4.5	3.7	A. C. Ivy
Illinois Central	110	2,763	90	15	10	16.6	9.7	3.2	H. Baugher
Chicago Fresh Air	104	307	91	2	0	2.2	6.8		
Chicago Lying-In	280	5,473	55	21	1	36.3	41.3	8.0	W. B. Serbin
Chicago General	60	No report	No report	No report	No report	No report	7.5		
Children's Memorial	175	2,287	197	74	...	37.5	35.4	23.1	W. G. Hibbs
Columbus Extension	75	No report	No report	No report	No report	No report	6.9		
Columbus	150	4,149	64	5	13	7.6	5.7	....	C. O. Getty
Contagious Disease (Municipal)	300	3,165	204	8	2	3.9	6.8	....	B. J. Kuly
Cook County	2,500	33,455	2,913	541	675	26.8*	12.7	8.9	W. B. Moody
Frances Willard	120	3,656	131	3	5	2.3	2.4	0.0	T. Moran
Garfield Park	70	2,271	33	0	5	0.0	0.0	0.0	Dr. Melsaac
German Evangelical Deaconess	68	No report	No report	No report	No report	No report	0.0	2.0	
Hahnemann	142	3,001	109	31	7	28.4	....	....	W. H. Wilson
Henrotin Memorial	75	1,688	38	1	1	2.6	....	....	J. A. Graham
Home for Destitute Crippled Children	110	1,122	1	0	0	0.0	0.0	0.0	
St. Anthony de Padua	185	4,238	195	5	7	2.5	1.2	4.7	F. B. Olentine
Isolation (smallpox)	35	249	3	0	0	0.0			
Mary Thompson	90	1,569	55	5	0	9.1	31.2	7.1	Norma Pyper
Lakeside	85	No report	No report	No report	No report	No report	11.4	0.0	
Mercy	395	6,059	221	63	25	28.5	13.0	....	Dr. Klemperer
Michael Reese	459	9,702	422	68	...	16.1	10.9	9.0	O. F. Schultz
North Chicago	85	1,900	49	9	3	18.3	5.8	?	B. H. Orndoff
Norwegian American	150	4,552	142	10	25	7.0	2.7	0.0	W. G. Hibbs
Passavant	75	2,487	96	No record	10	0.0	5.3	0.0	D. H. Ecke
Peoples	40	931	36	0	18	0.0	0.0	0.0	R. F. Zeit
Post Graduate	80	1,835	...	...	12	....	....	....	E. G. Kirk
Presbyterian	425	9,613	246	121	15	49.2	52.2	48.4	B. O. Raulston
Provident	65	1,406	78	4	9	5.1	....	....	J. Lewis
Ravenswood	44	1,600	36	2	5	5.5	19.6	13.6	J. J. Moore
St. Anne's	100	2,885	115	6	28	5.2	3.0	2.1	E. Weiss
St. Bernard's	200	No report	No report	No report	No report	No report	....	1.5	
St. Elizabeth's	225	4,289	210	15	12	7.1	1.6	....	L. A. Garness
St. Joseph's	180	4,650	167	29	1	17.3	18.1	21.4	W. Burmeister
St. Luke's	400	9,559	238	71	...	29.4	20.1	17.6	E. Hirsch
St. Mary of Nazareth	200	4,731	236	2	21	0.8	0.7	....	J. B. Lusk
U. S. Marine	125	1,422	6	3	0	50.0	16.6	21.4	
University (west side)	110	1,707	61	...	6	0.0	3.4	....	D. J. Royer
Washington Park	110	No report	No report	No report	No report	No report	No report	3.2	
Washington Boulevard	85	2,363	58	3	7	5.1	7.0	8.2	Dr. Householder
Wesley Memorial	275	6,587	191	45	8	23.5	15.3	7.9	J P. Simonds
West Side	155	5,421	152	0	16	0.0	0.0	0.0	R. L. French

* Percentage of available material. In calculating the percentage of permission necropsies at Cook County Hospital, coroner's cases have been excluded; in calculating percentages for other hospitals, coroner's cases have not been excluded, since some hospitals were unable to give the exact number of these. The percentages would be changed very slightly, however, by this adjustment.

uninformed undertakers, are urged as excuses for failure to obtain necropsies, and no doubt must be given due weight. These reasons do not explain, however, why it is that of 2 hospitals receiving the same class of patients distributed approximately alike as to race, intelligence and religion, in one hospital 30% of necropsies is obtained and in the other less than 5% or perhaps none. The real reason here is that no consistently sustained effort has been made by attending surgeons and physicians to obtain necropsies, and thereby to grow in their professional qualifications to render service to patients. It is hoped that in the coming year interest in necropsies and pathology may be further aroused, especially in those hospitals in which it is at present at a low ebb.

Within the last two years, the custom of holding weekly pathologic conferences at which the findings at necropsy and material from surgical operations are reviewed by the members of the staff has been extended so that at present several hospitals maintain such conferences, and find them to be among the most profitable activities of the staffs. A further extension of these conferences is recommended.

The committee desires to thank the superintendents and staffs of the hospitals for their continued cooperation in a survey whose only object is the improvement in the medical work of the hospitals themselves.

D. J. DAVIS
J. P. SIMONDS
A. B. KANAVEL
A. FRICK
E. E. IRONS, Chairman

THE ORTHOPEDIC NEEDS OF CHICAGO

REPORT BY SUBCOMMITTEE OF COMMITTEE ON MEDICAL NEEDS OF CHICAGO OF GOVERNORS OF INSTITUTE OF MEDICINE

The orthopedic need of any community is the adequate care of its orthopedic cases. Is that need met in Chicago? If not, how nearly is it met; what are the existing agencies, and what more is needed?

In general, the orthopedic service in the larger cities is much better than it is in the smaller ones, where, on account of economic reasons, orthopedic surgeons are less likely to locate.

How adequately the problem is met in Chicago can only be answered by a proper survey, which has never been made. The nearest approach to such a survey was recently made by W. T. Cross for the Department of Public Welfare of Illinois as a part of a comprehensive survey on "Rehabilitation of Physically Handicapped Persons," published in 1921. The portion of the report referred to details the number and kind of handicapped persons in a small area in a working class section as a basis of calculation of the number of handicapped persons in the whole city. In this limited selected area, 5% of the population were suffering from some kind of physical handicap. For the city, however, he estimates that 1.5% of the population handicapped would be closer to the proper figure. It must be understood that this survey takes in all kinds of physical handicaps, such as heart disease, various forms of tuberculosis, deafness, blindness, etc., and so offers a basis for orthopedic computation only where distinct orthopedic conditions may here and there be selected from the voluminous material gathered together in this comprehensive and valuable report.

Perhaps the best computation is to be based on the New York City survey of cripples made in 1920, and on the Cleveland survey made in 1916. In the New York Survey, a proportion of 6.9 cripples to 1,000 inhabitants was established; and in the Cleveland survey, a proportion of 6.2 per 1,000. An average of 0.65% of the population would therefore probably be a fair estimate for Chicago. This would yield about 17,500 as the number of cripples in this city.

In the New York survey, the following are some of the significant findings:

1. There are about 36,000 cripples in this city.

2. Of all cripples, about 50% are under 16 years of age; about 63% become crippled before reaching the age of 16 years.

3. Nearly one half of the cases discovered by the field canvassers were not being treated; over 50% of cripples are not known to any agency.

4. Very few cripples attend high school.

5. There are enough operative beds and sufficient clinical facilities, but insufficient number of convalescent and custodial beds.

6. In the social work for cripples, there are portions of the field uncovered, and at the same time somewhat vague limits assigned to the work of various agencies.

It is probable that these same significant findings apply with equal force to the Chicago situation and offer a substantial reason for a proper systematic investigation of our own present agencies for relief and the possible necessity of establishing others.

The New York survey was carried out on the working basis of the following summary of recommendations: elementary and secondary education, prevocational training, vocational guidance, medical and surgical treatment, convalescing care, custodial care, social service, home treatment, summer outings, vocational training, placement in employment, work in home and braces and appliances.

All agencies and institutions concerned with the many phases of the work with cripples were studied and their work correlated to reduce duplication of efforts and to supply actual needs. We need not be limited by this extensive program, but it offers many suggestions, which are amplified in the complete report, that should be of much value if we undertake a similar study here. This is a particularly opportune time for a complete report on the orthopedic situation in Chicago, as the appeal of the crippled and the handicapped is being responded to more earnestly and more wisely than it has ever been responded to before.

Influential organizations of philanthropic men and women anxious to aid these afflicted need the most careful direction of their funds and energies to secure the best results. Only a complete knowledge of the existing conditions permits them to attain the desired end, and only by a thorough canvass of the whole situation can this knowledge be obtained.

D. B. PHEMISTER
JOHN L. PORTER
CHARLES A. PARKER, Chairman

ANNOUNCEMENTS

At the annual meeting of the Institute, on Dec. 6, 1922, Dr. E. Wyllys Andrews, Dr. W. A. Pusey and Dr. J. B. Herrick were elected governors for five years.

At the annual meeting of the Board of Governors, on Dec. 11, 1922, Dr. William T. Belfield was elected president of the Institute; Dr. George H. Weaver, vice-president; Dr. E. E. Irons, secretary; Dr. J. A. Capps, treasurer, and Dr. L. Hektoen, chairman of the Board.

Dr. Theodore Tieken is chairman of the committee on admissions.

Dr. Harry S. Gradle has been elected fellow of the Institute.

THE PHYSIOLOGIC FUNCTIONS OF INSULIN

J. J. R. Macleod
Toronto, Canada

February 9, 1923

I wish to say that I consider it a great honor to be asked to address a society such as this, that stands for the best in medical science.

In introducing the subject which I have been asked to talk to you about tonight, I would like to remind you that the earliest investigations showing that there is a relationship between the pancreas and diabetes extend as far back as the seventeenth century, when Conrad Brunner showed that the pancreas could be excised in dogs without any definitely unfavorable symptoms supervening. The experiments were made with the object of showing that this gland is not essential for digestion, but incidentally it was noted that the animals behaved in a most peculiar manner. They exhibited definite symptoms of hunger and of diuresis. It is also interesting to note that an even earlier investigator, Malpighi, as a result of what he described as excision of the spleen, noted also in dogs that the animals exhibited symptoms which seem to have been those of diabetes. The chief outcome of Brunner's investigations was to divert men's minds from the pancreas, for it seemed from his results and those of his contemporary, Peyer, to be definitely established that this gland could have no essential function in the well-being of the animal. Even in the textbook of Johannes Müller, published during the first quarter of the nineteenth century, only a few paragraphs are devoted to the function of the pancreas; many pages, however, being devoted to the function of the stomach, for by that time the work of William Beaumont, done in this country, had become known in Europe. It was from clinical sources that the incentive to further investigation of the pancreatic function came. Cowley and Bright, and later the French physician Bouchardat, showed that there is a definite relationship between disease of this gland and diabetes in man. The belief in this association gradually grew; grew in that peculiar way in which impressions grow in every science, but particularly in medical science, and men's minds became more and more directed to the possible relationship between the pancreatic function and diabetes. Claude Bernard, among others, was attracted by this possibility, and although most of this master's work on the pancreas pertained to its digestive function, he also endeavored to seek for

its possible relationship to diabetes. He tried to remove the antidiabetic function of the gland in various ways—by injecting its ducts with oil or by ligating them, or by extirpating the gland—but he did not observe any symptoms like those of diabetes to develop.

About 1869, Langerhans, a pupil of Virchow, described the islands now know by his name, and some years later Kühne and Lea described their interesting blood supply. In 1889, von Mering and Minkowski made the epoch-making discovery that complete excision of the pancreas is definitely followed by the characteristic symptoms of diabetes. This great discovery naturally attracted widespread attention of numerous investigators: anatomists, experimentalists and clinicians. Anatomists, such as Laguesse and Diamare, contributed the most important work at this stage, and many experimentalists repeated Minkowski's observations and supplied important confirmation of the results. Minkowski had suggested in a paper published in 1892 that removal of the pancreas must result in the removal from the body of something that is necessary for the metabolism of carbohydrates, but he was rather vague as to what this something might be. The statement that it was an internal secretion was first definitely made by Lepine, with whose work you are probably more or less familiar. That the pancreas produces an internal secretion having to do with carbohydrate metabolism and with the regulation of the blood sugar came to be generally recognized, particularly because about this time the conception of internal secretions had taken firm root through the discoveries of thyroid and of suprarenal extract. The anatomists pointed out that the structures in the pancreas that are probably responsible for this internal secretion of the gland are the islands of Langerhans.

Stimulated by the work of these investigators, many attempts were made to put the hypothesis to the crucial test, which in this case is obviously to administer an extract of the gland to animals rendered diabetic by its removal. The fact that the removal of a gland is followed by certain symptoms, as is the case with the pancreas and the symptoms of diabetes, is no proof that the gland produces an internal secretion, for it is obvious that the removal may cause the symptoms merely because the blood can no longer circulate through the gland where normally some toxic substance is removed from it.

These early attempts at the administration of pancreatic extracts were more or less failures, and it was not until 1908 that a really successful extract of the pancreas was produced. In this year, Zuelzer, a

German investigator, prepared an alcoholic extract that was capable of removing certain of the symptoms of diabetes in laboratory animals and also in man. He showed that this extract could, for example, be used as an antidote for the hyperglycemia that is produced by epinephrin. Six patients with clinical cases were also treated with Zuelzer's extract. Several of them showed favorable results. Most of the symptoms of diabetes were temporarily removed, glycosuria and acetonuria particularly. The subjective condition of several of the patients was also definitely improved, but, unfortunately, in other cases toxic symptoms supervened, so alarming in their nature, that the treatment was abandoned. The subject seemed to be closed by the unfavorable results published by Forschback from Minkowski's clinic, and as a result clinical interest in pancreatic extracts almost entirely disappeared, and the possibility that an internal pancreatic secretion might exist came to be the problem of the experimentalists. Among these were Knowlton and Starling who, about 1912, succeeded in showing that the addition of pancreatic extract to the fluid perfused through the isolated heart removed from diabetic animals is capable of increasing to some extent the power to utilize sugar. Such results were not obtained in a sufficient number of experiments, however, to make them convincing.

The work then came to this country. Stimulated by Knowlton and Starling's reports, Murlin, Kramer, E. L. Scott and Kleiner took up the problem, each of them attempting to solve it by preparing extracts of the pancreas, by various methods, and studying their effects on diabetic (depancreatized) animals. These investigators made the fatal mistake of observing only one symptom of diabetes at a time, instead of observing two symptoms, and I believe that had they insisted on this criterion they would have been sufficiently convinced from their results that they really had demonstrated the hormone, that they would not have abandoned their researches.

The most important of all the work that was done in this country was probably that of Clark, then working under Prof. W. G. McCallum in the pathologic laboratory at Johns Hopkins. Clark made investigations on the effect of transfusing a saline solution through the pancreas and then through the heart. He found that if he transfused Locke's solution containing sugar through the heart before sending it through the pancreas that the rate of sugar consumption was relatively slow. If, on the other hand, he transfused this solution first through the

pancreas and then through the heart, the rate of sugar consumption became markedly increased—an excellent demonstration, showing that by transfusing sugar through the pancreas something becomes added to it that activates the sugar consuming power of the heart and makes it possible for more sugar to be used in a given time. Later he made another discovery, namely, that although by transfusion through the pancreas alone there is no change in the amount of sugar as estimated by the reduction methods, yet an alteration takes place in the rotatory power of the sugar. This indicates that the sugar must become changed in some way: must become in some way prepared for combustion. Evidently this has some bearing on the ultimate consumption that takes place in the heart, and it conforms with the more recent work of Hewitt and of Winter and Smith, which will be alluded to later.

This leads us to the experiments which were made by Dr. Banting and Mr. Best in the Physiological Laboratories in Toronto. Since Dr. Banting describes these experiments to you, I will pass on to review briefly some of the anatomic feats regarding the pancreas upon which the experiments of Dr. Banting and Mr. Best depended.

It has been known as a result of the observations of many investigators that ligation of the pancreatic duct when it is properly performed is followed shortly by a degeneration of the pancreatic tissue involving first mainly the zymogenous cells. Later, however, the island tissue also becomes involved. At a certain stage both the zymogenous tissue and the island cells are in a state of degeneration, but very early these tissues begin to be replaced by new tissue. These processes of degeneration or destruction and of regeneration go on in both the zymogenous and the island cells for many weeks, at least in the case of the rabbit, in which accurate observations have been made. Ultimately, however, it is the island tissue that alone remains. The zymogenous tissue gradually disappears until finally, in about 550 days, in the rabbit, there remains practically nothing but island tissue (Clark and Bensley). It is a most interesting thing that this regenerated island tissue is definitely related to the duct system and, that in place of being scattered in small nodules through the pancreas, it extends along the duct system, just as Dr. Slater Jackson has found it to be in the more primitive pancreas of the skate. It is for that reason that I call your attention to the peculiar distribution of the islet tissue in the pancreas of the skate. These facts raise the question as to possible regeneration of islet cells in the diseased gland. It is evident, I think,

that if a degenerated pancreas many, many weeks after ligation of the ducts is capable of regenerating fresh island tissue from the tubules, the same thing is likely to happen when the gland has been destroyed by disease, provided this has not involved the gland so extensively that no healthy duct cells are left. Where the gland is completely destroyed so that its duct system, as well as its secreting cells, have been destroyed, then no hope of regeneration can be entertained. When, however, this process has not yet caused complete destruction, it seems reasonable to expect that if we can rest the gland, either by dietetic treatment or by the administration of insulin, there is a chance that regeneration may be possible.

Banting and Best took advantage of these facts to prepare an extract of pancreas that would not contain the proteolytic ferment, trypsin, by whose action, in the extracts of the intact gland, they assumed destruction of the hormone would occur. They found that this extract lowers the percentage of sugar in the blood and diminishes the amount of sugar in the urine in depancreatized dogs. By extraction of the intact gland with alcohol, they also found that the antidiabetic hormone was sufficiently preserved, and later J. B. Collip succeeded in isolating from such extracts, by precipitation with alcohol, higher concentrations of a fraction which could be used for administration to patients without causing local irritation.

The investigation at this stage was greatly advanced by the discovery that the blood sugar of normal rabbits is also affected by injection of the purified extracts, to which the name insulin now came to be given—a name previously suggested for the then hypothetical hormone by Sir E. Sharpy Schafer.

(Here charts were shown illustrating the effect on the blood sugar of normal rabbits following the injection of extracts.)

It was also observed that the injected animals developed symptoms (convulsions), and that these symptoms appeared almost invariably when the blood sugar had fallen to somewhere about 40 or 45 mg. %. Occasionally, so definite a parallelism between the convulsions and the percentage of blood sugar was not observed. Sometimes, for example, the convulsions appeared when the blood sugar reading was only 60 mg., or they might fail to appear, though it was considerably below 40 mg. If we take the average of a great many results, we find, however, that convulsions appear almost invariably at about 45 mg. of sugar. These convulsions are quite characteristic. The animal shows

clonic convulsions of its musculature, which occasionally involves the whole of the body, and during this condition the animal, with its head retracted, throws itself about, often in a violent fashion, exactly as when an animal has been spun around and thrown on the floor. This would seem to indicate that there must be violent stimulation of the labyrinthine apparatus, the apparatus responsible for the control of equilibrium. The convulsions usually last for the best part of a minute, sometimes longer, and then the animal lies in a collapsed state, sometimes unconscious, breathing rapidly, the head usually retracted. It may lie in this condition for several minutes, and then a second convulsion supervenes. These convulsive seizures, alternating with periods of coma, may go on for several hours before the animal dies. It eventually dies of respiratory failure. The animal often become highly excitable before the actual convulsive seizures appear. The association between the incidence of these symptoms and the percentage of blood sugar indicates that the two must be correlated. The symptoms must be related to a lack of blood sugar. To confirm this we studied the effect on the symptoms of the injection of glucose. We found that the symptoms were immediately removed. There is nothing more striking that I know of in the physiological laboratory than to see the disappearance of those violent symptoms within a minute or so after the subcutaneous injection of glucose. No other blood sugar has an effect nearly so satisfactory. Levulose, mannose and galactose may diminish the symptoms, but they have not such a definite inhibiting effect as glucose. None of the dissaccharides injected subcutaneously or intravenously has any effect at all. Alkali has no effect. Nothing that we have tried, except glucose, definitely removes the symptoms except epinephrin, which, of course, mobilizes glucose in the body. This shows definitely that the symptoms are related to the lowering of the percentage of glucose in the blood. It does not necessarily mean that they are directly due to the lowering of glucose; it merely shows they are closely related to it. Possibly something toxic develops in the body, particularly in the nerve cells, the development of which in the normal animal is prevented by a certain concentration of glucose or one of its close derivatives in the nerve cells, but that is a matter which needs further investigation. One cannot decide that by examining the blood. It is an intracellular process, not one that will involve the hydrogen-ion concentration of the blood. In this connection it is significant that injections of alkali do not relieve the symptoms.

Having demonstrated these facts for normal rabbits, the next thing was to find whether insulin is capable of preventing the various forms of hyperglycemia that are known to physiologists. Claude Bernard was the first to show that puncture of the floor of the fourth ventricle has the effect of causing marked glycosuria, but we found that insulin almost entirely prevents it, as well as the hyperglycemia which is its immediate cause. Various investigators, Stewart, Rogoff and others, have shown that asphyxia always causes a marked hyperglycemia, but we have found that it fails to do so in animals injected with insulin. One form of asphyxial hyperglycemia that is quite common is that due to poisoning by carbon monoxide. Carbon monoxide in our experience, however, does not produce hyperglycemia after the administration of insulin. It may cause a slight rise. Ether also fails to cause the usual degree of hyperglycemia when it is given to rabbits injected with insulin. This is interesting in connection with surgical operations on diabetic patients since it must diminish the dangers due to hyperglycemia which are more serious in these than in normal patients. It is of practical importance to know that insulin will diminish the degree of ether hyperglycemia and thus diminish the risk. Another type of hyperglycemia that is well-known to experimentalists is due to the subcutaneous injection of epinephrin. In this particular case it is clear, since you can grade the dose of epinephrin and also the amount of insulin that is capable of presenting it, that it might be possible to determine the dosage of insulin in terms of extent to which it can prevent the hyperglycemia due to epinephrin.

We studied the effect of insulin on diabetic dogs in greater detail than was possible at the time Banting and Best conducted their original experiments. The symptoms I wish to call to your attention are: first, the respiratory quotient, second, the glycogen metabolism, and third, fat metabolism. These were the three problems that Banting and Best could not investigate while they were at the main problem of ascertaining whether or not it was possible to isolate a pancreatic hormone. In regard to the respiratory quotient, you will remember that this expresses the relationship between the amount of carbon dioxide exhaled and the oxygen inhaled in a unit of time. It is a ratio which tells us the kind of food that is undergoing metabolism. When carbohydrates are undergoing combustion, the respiratory quotient is unity; there is as much carbon dioxide given out as oxygen taken in, for the reason that carbohydrate consists essentially of carbon *plus*

hydrogen and oxygen in the same proportion as in water (CH_2O). From the combustion point of view, therefore, we may regard the molecule as being just so much carbon. When C is burned by O_2 the volume of O_2 that is used is equal to the volume of the CO_2 produced; therefore the respiratory quotient must be unity. It is different with fat and protein. In the case of fat and protein, oxygen is required, not only for the carbon, but for part of the hydrogen as well; therefore the volume of oxygen which is used will be greater than the volume of carbon dioxide which is produced. The respiratory quotient, therefore, is less than unity, and it is one of the achievements of modern medical science, due to the work of Rubner, Lusk, Benedict and others, that it is now possible to tell precisely from the respiratory quotient what type of combustion is going on in the body at a given time; what portion of protein and what portion of carbohydrate is being burned. One may define diabetes as the inability of the body to burn carbohydrate. This means that the administration of carbohydrate to a diabetic patient will not cause the respiratory quotient to rise to the same extent as in a normal animal. There is no alteration of the respiratory quotient when diabetes is extreme, such as in the case in diabetic dogs. If you feed diabetic dogs with carbohydrate, for example, there is little or no change in the respiratory quotient. If insulin be given with sugar to a diabetic dog, or patient, however, the respiratory quotient rises as in a normal person. That, then, is a fundamental observation showing that insulin makes it possible for the sugar to be burned up. Now this is the last link in the chain of metabolic processes through which carbohydrate passes in the animal body, and the first link, as you all know, is the deposition of glycogen. In diabetes, both in laboratory animals and in man, no glycogen, or only a trace, is deposited in the liver, no matter how much sugar you may feed to the animal. If you give insulin with sugar, however, glycogen becomes abundant in the liver. In some experiments on diabetic dogs, we have observed over 12% of glycogen in the livers, and in one case, over 20% was found. This is the highest percentage of glycogen that had been observed in any animal up to this time. This shows that insulin acts on the glycogenic end of the metabolic chain of carbohydrate as well as on its oxidative end. How these two processes are linked together we do not know, but that the two are affected together are obviously most significant facts.

With regard to fat metabolism, it is well known that in diabetes the process goes seriously wrong. In the first place, the transportation of fat is affected so that the blood and the liver become loaded with this substance. The resulting lipemia is a serious symptom in diabetes, but it quickly disappears on the administration of insulin. In the second place, the combustion of fat which is at the other end of the metabolic chain is seriously deranged in diabetes. In a normal animal the combustion of fat proceeds by stages. The long fatty acid chain is broken off bit by bit by oxidation at the so-called beta C. atom, and the end products of this combustion are water and carbon dioxide. There is a stage in the breaking down process, however, at which it is apt to hesitate, that is, at the stage of butyric acid ($CH_3CH_2CH_2COOH$) which, it will be seen, contains four carbon atoms. In diabetes butyric acid, instead of becoming completely oxidized, becomes so only as far as beta-oxy-butyric acid ($CH_3CHOH\ CH_2COOH$) and the closely related acetocetic acid and acetone, which are responsible for the symptoms of coma. It is said that this hesitation in the final oxidation of fatty acid is due to the fact that there is no carbohydrate combustion going on. Fat burns in the fire of carbohydrates, and since in the diabetic no carbohydrate is being burned, fat combustion also becomes incomplete. It smokes as it were, and the smoke accumulates in the body in the form of beta oxybutyric acid. Since insulin affects the combustion of carbohydrates, it should also affect this ultimate combustion of fat, and such has been found to be the case. Insulin stirs up the carbohydrate fires so that fat combustion proceeds to its completion, and the so-called acetone bodies disappear from the urine.

Finally, let me allude briefly to some work which we are engaged in pertaining to the mechanism of the action of insulin, but which is as yet incomplete. When rabbits are injected with varying quantities of insulin, it is remarkable how, during the first half hour after injection, the blood sugar always comes down at nearly the same rate. This would seem to indicate that the process by which the blood sugar becomes lowered must be an intravascular one. It looks as if it must be something occurring in the blood itself. There are two reactions that might occur in blood itself: One is glycolysis, and the other is a union of sugar with something else, or its polymerization into glycogen. If blood be removed from the body and insulin added to it, the rate of glycolysis is not altered. Neither is the rate of glycolysis different

in the blood of a normal rabbit and in that of one previously injected with insulin. There is, therefore, no evidence that insulin influences the rate of glycolysis. The evidence of union of the glucose is also lacking, for if blood be taken from an animal when the hypoglycemia is marked and hydrolyzed by heating with acid, there is no greater increase in reducing power than occurs in normal blood.

The conclusion is that insulin passes into the tissues where it creates, as it were, a vacuum for sugar, with the result that sugar is withdrawn from the blood more quickly than the loss can be made good by the mobilization of sugar from the glycogen of the liver. There is a sudden drainage of the sugar from the blood to fill up the vacuum for sugar in the tissues. That narrows the question down to this: What is the cause of the sugar vacuum in the tissues? There are several possibilities. One is that the sugar is oxidized; another is that it is reduced into a fat-like substance; and a third that it is converted into glycogen. With regard to oxidation we have seen that the respiratory quotient is quickly raised when insulin is given to diabetic animals, indicating that the combustion of sugar is encouraged. That does not necessarily mean, however, that insulin would have the same effect in normal animals. This had to be specially investigated, which has been done by Mr. Pember and Mr. Dickson, who have demonstrated quite clearly that the respiratory quotient in normal animals is definitely raised by giving them insulin without any sugar. Not only that, but the energy output under these conditions becomes greatly increased, at least in dogs. The behavior of the respiratory quotient in many of these experiments was remarkable, for it rose to well over unity and remained there for an hour or two. This may be due to a reduction of carbohydrate to fat, such as occurs, for example, in hibernating animals who eat great quantities of carbohydrate-rich food in the fall months and store it away as fat, during which time their respiratory quotient is well over unity. These respiratory experiments, therefore, indicate that there is increased combustion and that there is a change in the nature of metabolism. With regard to the third possibility, namely, the deposition of glycogen, the fact that insulin causes this to occur in the diabetic dog does not prove that it will also occur in the normal animal. As a matter of fact, we can obtain no evidence that it does, although we have paid much attention to the problem.

Regarding methods for the assay of insulin I may say that we are trying hard to work this out on a satisfactory basis before insulin

will be available to every one who wants to use it in the treatment of diabetes. At present we define as one physiologic unit the amount that will lower the blood sugar of rabbits, starved for 24 hours, to the convulsive level (0.045%) within 3-4 hours. The clinical unit is one third of this strength, because it has been found that some clinical cases benefit by one third the physiologic unit, and it is thought advisable to avoid fractions in dosage. It is difficult in using normal rabbits, however, to obtain accurate results, and Dr. Eadie has been trying to work out a more precise method by ascertaining to what extent insulin will prevent the hyperglycemia due to injections of glucose or injections of epinephrin.

Finally, let me allude to some experiments by Miss O'Brien and Mr. McCormick bearing on the possibility that the internal secretion of the islands of Langerhans, insulin, is controlled through the vagus nerve. Stimulation of the splanchnic nerve causes an increase in blood sugar, and the question arises whether the vagus by increasing the output of insulin might cause a lowering of blood sugar. Although many of the results are negative in character, there are some that clearly show a lowering of blood sugar following stimulation of the vagus.

With regard to the fundamental cause for the action of insulin, what does it do? Why does it cause glucose to be used up? The answer may be furnished by the experiments of Hewitt and Pryde, and, more recently, of Winter and Smith in England. The former observers have shown that ordinary glucose is converted into another form of glucose (gamma) when it comes in contact with living tissue cells. Ordinary glucose is called alpha-beta glucose and has a specific rotatory power which remains constant and corresponds to the reducing power. When this alpha-beta glucose comes in contact with insulin and certain tissue constituents, some gamma glucose is formed, as is indicated by a lowering of the dextrorotatory process. Clark also found by transfusing Locke's solution containing glucose through the pancreas that, although the reducing power was not altered, its polarizing power became slightly lowered. It is interesting that Winter and Smith have recently announced in the British Medical Journal that insulin is a substance which activates an enzyme derived from the liver to produce gamma glucose; that is, the combination of alpha and beta glucose *plus* liver extract *plus* insulin causes a production of gamma glucose. What the ultimate outcome of this experiment of Winter and Smith may be is difficult to say.

THE VALUE OF INSULIN IN THE TREATMENT OF DIABETES

F. G. Banting, M.D.
Toronto, Canada

February 9, 1923

The work commenced with an idea which presented itself from reading an article by Moses Barron in "Surgery, Gynecology and Obstetrics" in November, 1920. In this article, Dr. Barron described the degenerative changes that occurred in the human pancreas following blocking of the pancreatic duct by gallstones. Such degenerative changes would occur in animals following ligation of the pancreatic duct. The literature was reviewed, and it seemed to be the common belief that the acinar cells which secrete pancreatic juice degenerate for the most part following this operative procedure, that they are replaced by fibrous tissue at the same time, and that the islands of Langerhans remain intact for the most part. Animals, although they are deprived of their external secretion, retain their internal secretion and do not become diabetic. It seemed that in this way we might be able to get rid of the external secretion and make an extract of the internal secretion free from trypsin, lipase and amylase. The physiological interest of this hypothesis was recognized by Professor MacLeod in an interview at that time, but the work was not commenced until the middle of May, 1921. At that time, Mr. Best and I commenced with the ligation of the pancreatic ducts in a number of dogs. We allowed an interval of from 6 to 10 weeks for the degeneration of acinous tissue to occur, and then removed the remnant and made sections that showed degenerated acinous tissue and normal healthy islands. Extracts were prepared by cutting up this degenerated pancreas into small pieces and grinding in a mortar in ice cold Ringer's solution, filtering until almost clear, and injecting into the vein of a depancreatized dog. After the pancreas is removed the dog develops a severe and fatal form of diabetes. The blood sugar becomes elevated from its normal level of 90 mg. within 24 hours to possibly 250 mg., going up on the third day to the neighborhood of 300 mg. At the same time, the dog develops a severe form of glycosuria, excreting large quantities, as high as 25 gm. of sugar, on a meat diet, or even more if carbohydrate is added to the diet. The wounds do not heal rapidly. The

dog becomes sleepy and quiet. A scum gathers in the corners of the eyes about the 4th, 5th or 6th day. Rarely do untreated animals live beyond the 12th day, although some observers have reported animals that lived as long as the 20th or 21st day. Extract prepared in the manner described was given intravenously to such a dog, and the blood sugar, observed at various intervals following injection, as well as the amount of sugar excreted in the urine, was reduced greatly.

The first series of experiments was carried out as described. The next type of extract used was obtained by exhausting or endeavoring to exhaust the pancreatic juice by long continued injection of secretin into the femoral vein of a normal dog. The pancreas was removed after secretin had been injected for 6 hours, and an extract made in a similar fashion to that used in making injections of degenerated gland. Following this there was also a marked lowering of the percentage of sugar in the blood from a high level of 300 mg. to 70 mg. On continued injection for some time blood sugar remained at a subnormal level, and the dog was sugar-free. However, extracts of the pancreas are not always constant either in their potency or in the amount of toxic substances which they contain. The method was abandoned almost immediately because of the toxic effects. There was no great improvement on using extracts of the whole gland as did Kliner, Moleska and other observers.

The next type of extract was obtained by macerating a fetal pancreas. As Leguis had found, there are comparatively larger numbers of island cells in the pancreas of the fetus and new born than in the adult pancreas. It seems reasonable to obtain the pancreas from new-born animals. On further thought, it seemed reasonable that that would be the time when no external secretion would be present, but since all internal secretions are present during intra-uterine development that there might be present then an internal secretion of the pancreas. Mr. Best and I succeeded in getting nine pancreases from young fetuses. An extract was made and injected intravenously into diabetic dogs. All these extracts for the first six or eight months were tested on diabetic dogs. We obtained a marked fall in the percentage of sugar in the blood and did a great number of other experiments. We repeated the observations that we had previously made on other forms of extracts, but the great value of the fetal gland extract was in the fact that we could obtain it in abundance. It gave us a chance to try to extract the active principle by other means. We

tried 95% alcohol with sufficient hydrochloric acid to make the solution 2% acid. Equal volumes were mixed with the fetal pancreas and an extract made. However, it was necessary to get rid of the alcohol, and this was done by evaporating it and redissolving the residue in distilled water and injecting it. Extracts made in this manner were potent and contained an active antidiabetic principle. The purpose in the use of these principles was to obtain some substance that would dissolve the toxic substance that we wished to get rid of, so this solvent could be adapted to the extraction of the active principle from the whole gland. The whole gland extract was made by the adoption of this principle, and a marked reduction in blood sugar was thus obtained. These were refined extracts sufficient to permit tests on 3 persons with diabetes. Unfortunately, our extracts contained too high a percentage of protein, and there occurred at the site of injection, in 2 instances, cold abscess from unabsorbed protein.

Our first attempt at longevity resulted in prolonging the life of a totally depancreatized dog for 19 days. This dog died in a peculiar fashion. We had made a new batch of fetal calf pancreas extract and injected it intravenously. About 2 hours after injection the dog developed an anaphylactic-like reaction. We called it an anaphylactic-like reaction, but we could not understand how anaphylaxis could occur in this dog, because it had been receiving in previous doses extract of the same material. The dog showed marked symptoms beginning with drowsiness, finally going into coma and then marked twitching and slight foaming at the mouth. The dog was given up for dead, but on the following morning it was up walking about. The next day a smaller dose of the extract was given, and symptoms occurred similar in type but earlier in point of time, coming on about an hour after injection. They were much more severe, and from this attack, which we now consider to be hypoglycemic, the dog did not recover. Unfortunately, we did not make a blood sugar estimation, as we were simply reserving this dog for longevity. A second attempt at longevity resulted in the dog living 21 days. This dog had been tried much earlier and died because we were unable to obtain the extract. A 3rd dog, although it became very thin and emaciated, possibly from lack of external secretion of the pancreas and its ability to absorb food from the intestine, was able to run about on the 70th day following removal of the pancreas. It had been given, at first, 3 injections, but later 2 injections a day, and finally one injection a day throughout

the 70 days. On the 70th day the dog was chloroformed and a careful necropsy immediately made by Dr. Robinson. A careful search was made for any pancreatic remains, and none were found. The only possible pancreas cells were small plaques measuring about 2 inches in diameter and 1.5 mm. in thickness, lying between the muscular layer and the mucous layer, that is, inside the lumen of the intestine. These plaques closely resembled island cells. Serial sections were made, but no island tissue was found.

About this time in the development of the extracts, Mr. Best and I became associated with Dr. Collip, professor of biochemistry in Edmonton University. Dr. Collip succeeded in producing an active principle. We had found that the active principle was insoluble in 95% alcohol, that it was soluble in alcohol up to 65%. Dr. Collip ran squarely between these two points and succeeded in producing an active principle. This made a great contribution to the knowledge of the active principle. After this, the clinical work was followed by Dr. Campbell and Dr. Fletcher under the direction of Dr. Graham. Dr. MacLeod took over the physiologic portion. The manufacturing was taken charge of by Professor Lefrest, and the work carried out by Dr. Collip.

The clinical investigations followed closely in the footsteps of the physiologic investigations. The first cases tried were simply confirmations of the fact that the human diabetic patient could be rendered sugar-free, that the blood sugar could be rendered normal, that the acetone bodies could be burned up or eliminated from the blood and urine, and that the patients were clinically improved. The respiratory quotient was at first done in the physiologic laboratory. This could be raised by the administration of extract from a low level to a high level of 9.2, showing definitely that the carbohydrate could be burned following the administration of extract. The clinical investigation, however, was unfortunately interrupted by difficulties in the production and was next resumed in a clinic established with Dr. Gilchrist in the Christie Street Hospital for disabled soldiers. We owe a great debt of gratitude to the spirit with which the men entered the research, because at that time our extracts contained irritating properties and were not always potent, but rarely did the men hesitate. However, I will not dwell on the slow development that occurred from these months on but will describe the present routine of management of a case of diabetes in the clinic as it is now established in the Toronto General Hospital in the Department of Medicine in the University.

When a patient is admitted he remains on the diet on which he was living previous to admission for the first 24 to 48 hours. This is of value in estimating the tolerance of our patients. After this short trial period, the patient is placed on a well-planned diet, such as the Woodyatt formula or the Wilder formula, a diet so planned as to give the greatest amount of calories for a minimum amount of carbohydrate, thus making the best use of fats and enough protein to meet the nitrogenous requirement. The patients remain on this diet for from 6 to 10 days. At the end of this time they usually become sugar-free, if the cases are mild, or amenable to any dietetic treatment. If the cases are severe, they do not become sugar-free, but the output of sugar comes to a fairly constant level and the average amount of sugar excreted can thus be estimated. If the patient becomes sugar-free on this basic level diet, and if we are able to increase this diet by one-eighth to one-half of its caloric amount, we do not consider the condition sufficiently severe to require insulin treatment. We have a large number of patients, and in this way we eliminate the mild type of case and only treat the severe cases. Thus we have nothing to report on the vast majority of diabetic patients, and an important field is left for further research on the method of treating the more severe cases. We cannot, therefore, say anything with regard to the mild type of diabetes. We check over the blood sugars, the amount of sugar excreted, the acetone bodies, the nitrogen and urea output during this 6 to 10 days' trial period. We are then in a position to judge the severity of the case and the amount of carbohydrate that the patient can burn with insulin and carbons from his own pancreas. If a patient, let us say, is excreting on an average of 10 gm. a day at the end of this time, we commence insulin treatment by giving just enough insulin to render him sugar-free. This brings up the question of the dosage of insulin. It has been one of our greatest difficulties to estimate the requirement for the patient. At present the procedure is to carry out a physiologic assay in the laboratory by finding out the blood-sugar reducing power of any given simple extract. This gives us a rough estimate of the potency. The next step in the assay of the potency of the extract is to give the patient whose tolerance is definitely known and who has been followed for some time, 5 units of insulin to find out the difference in the amount of sugar excreted in the urine if he is not sugar-free. We find out how many additional grams of carbohydrate the patient can tolerate with the addition of this

dose of insulin. In this way, we estimate the gram equivalent of any given batch of extract, giving the gram equivalent or the numbers of grams that can be accounted for by a given amount of insulin, and we can transfer this knowledge gained from our own patients with known tolerance to our new patients. We give a dose of say 10 units, which is just the amount for a man who is excreting on this basic level diet. The next step is to increase that diet and to increase the amount of insulin administered; by carrying this on step by step we can greatly increase the caloric intake of our patient, and if we have a good extract and are fortunate in planning the amount of extra calories given to the patient with the amount of insulin administered, we can keep the patient sugar-free and at the same time increase his diet two or three times above his previous tolerance.

Dosage is one of our greatest problems at this time. An overdose is a serious consideration, because with an overdose there is a state of marked lowering of the percentage of sugar in the blood so that the patients develop the same type of reaction as do laboratory animals. Hypoglycemic reaction in man is characterized by hunger. This may be marked in some patients and much less marked in others. There is frequently flushing and profuse perspiration. This is not a constant symptom but one frequently observed in children. It is followed by lowering of blood pressure and by pallor. Once a patient has experienced a hypoglycemic reaction he does not fail to recognize the onset of a second reaction. A patient 6 or 8 years old was able to tell his mother of the onset of the reaction. The patients describe it as a drowsiness which is followed by a feeling of tremulousness, and when there is no visible tremor the patient feels trembly. If the overdose is great, the patient goes on through these symptoms and becomes mentally irrational, the language incoherent. The patient may get up and walk about, but he finally becomes drowsy and goes into coma. The fortunate thing about a hypoglycemic reaction is that an antidote for this reaction is easily procurable. In mild cases, glucose is administered in the form of orange juice with a little glucose, or straight orange juice, or glucose candy, or anything that contains glucose and is easily given by mouth. This will entirely remove the symptoms and the subjective sensations. The response to glucose is rapid. The patient feels entirely relieved in from 3 to 5 minutes. However, recently since insulin has become much more refined, the absorption is much more rapid, and the symptoms often come on so rapidly and

sometimes in patients who have not previously had reactions and therefore do not recognize it, that they go into coma before means are taken to prevent it. In these cases, the best treatment is subcutaneous administration of from 10 to 15 minims of epinephrin. Epinephrin often draws out enough glycogen from the liver to increase the percentage of sugar in the blood and therefore relieve the symptoms. Formerly we gave intravenous injections of glucose, but that is not convenient. It is an easy matter to administer epinephrin. When the patient comes out of the coma he is given glucose by mouth. Patients recover from severe coma in 3 to 5 minutes and sometimes in a shorter time. We are constantly living in dread of severe hypoglycemic reactions occurring at night, and consequently when we are changing from one batch of insulin to another we warn the patient closely regarding signs of an overdose, or in commencing the treatment in new patients they are also warned. The treatment usually consists in at once differentiating between a hypoglycemic reaction from an overdose of insulin and a hypoglycemic reaction from too much food. The treatment consists in retaining the patient with normal blood sugar and sugar-free. In cases of long standing, this procedure is more easily carried out. When the diet is greatly increased, it is more difficult to balance the hypoglycemic and the hyperglycemic blood sugar levels. It is possible, however, to just strike this balance, and the easiest method is to place the paient on a diet that may be adequate to meet all the requirements of strength and growth and to give just sufficient insulin to account for the difference between that diet and the patient's natural tolerance. In one case, that of a patient with severe diabetes, the patient gave herself insulin and examined her own specimen and was able to keep free from hypoglycemic reactions and free from sugar for 31 days on one large batch of extract. The patients learn to balance themselves on the extract and to give just enough to obtain the required effect, just as digitalis can best be administered by the patient himself according to the way he feels. The time of administration is not completely settled. The most rational time for the administration is from within 20 minutes to half an hour previous to a meal. The reason why this appears to be most rational is that in a normal healthy person the pancreas is stimulated to pour insulin into the blood stream as the food is being absorbed from the intestine, and if we give insulin just previous to the meal, there is absorption from the artificially administered insulin at the same time the food is being absorbed in the intestine, thereby maintaining the patient sugar-free.

The methods of administration have been various. Subcutaneous injection has appeared to be best so far. We tried administration by mouth, by rectum, intramuscularly, intraperitoneally, intravenously and by inunctions, rubbing into the skin. We have tried it in various forms and various mixtures, and the best results were obtained by subcutaneous injection. This is a little detrimental because of the slight pain at the time the injection is made, but the patients are willing to endure the pain of subcutaneous injection provided they are allowed an increase in diet. We have sometimes a slight local reaction at the site of injection. Formerly, there was a general reaction of an anaphylactic nature.

Possibly if I describe in detail the treatment of one case it will give a better understanding of the general management ,and it will also illustrate a point with regard to toleration following long continued injections of insulin. In April, 1919, at the age of 12½ years, glycosuria was first noticed in this patient. The patient was immediately placed on a restricted diet by Dr. Allen. By carefully adjusting this diet and by continually observing the patient she was kept sugar-free, with a rare trace of sugar in the urine and acetone-free until August 16, when she came to Toronto to commence insulin treatment. At times her toleration was so low that the diet had to be decreased to 5 or 10 gm. of glucose per day. However, on arrival in Toronto the toleration was slightly increased from what it had been 6 months previously, and we were able to raise the caloric intake from 833 calories per day to 933 calories per day, the diet consisting of 20 gm. of carbohydrate, 35 of protein and 71 of fat. The patient had been on this diet for some months, and 2 weeks previous to coming to Toronto an attempt was made to increase the diet by the addition of 10 gm. of fat. The plan was to increase the diet by the addition of 1 or 2 gm. per day, stretching the total of 10 gm. over a week at a time. On the eighth day, when 9 gm. of fat had been added, sugar appeared in the urine, and the patient was placed on the former diet of 933 calories. On arrival in Toronto, the treatment was commenced by giving her one augmented meal per day and one dose of insulin. On the day she was sugar-free, she was given, in addition to her usual meal, 10 gm. of carbohydrate, 10 of protein and 25 of fat and just sufficient insulin to react for this addition in diet. At the end of a week we gave her 2 augmented meals and 2 doses of insulin, 20 minutes before each meal, and then by gradually increasing these augmented meals and

increasing the doses of insulin we raised her caloric intake to 2,512 calories. During this procedure she remained sugar-free, except for a small trace on 3 different occasions in the past month. She gained rapidly in weight, and her general clinical condition was markedly improved. She had lost in weight during her 3 years' illness from 81 to 45 lbs. She gave a typical picture of a severe diabetes, with dry, scaly skin, dry hair, sunken chest, large protruding abdomen, very thin legs and arms and slight edema of the feet and ankles. At the end of a month after arrival she was able to walk about the room slowly, could rise from the chair and had gained some 8 or 9 pounds in weight. At the end of 3 months she had gained 31 pounds in weight and was able to take quite strenuous exercise. She was taking Swedish exercises to develop the abdominal muscles; she was beginning to get some color in her cheeks and was beginning to feel very much stronger. The subjective sensations in such a case are marked; the patients feel much stronger and better, and have a better outlook on life. The outlook becomes that of an optimist. After this gain in weight after 3 months, she was placed on the former diet of 933 calories, and we endeavored to increase her intake by adding fat in some form. The fat was added in the same way that it had been before she came to Toronto, except that instead of adding 9 gm. before sugar appeared in the urine only 8 gm. were added. In other words, her toleration was not increased. The treatment has continued up to the present time. The child was trained in the use of the extract, and she now plans her own diet, gives her own extract and examines her own specimen. She is given as high as 800 units at one time, and she balances her diet, that is, she knows the proper amount to take to just maintain herself sugar-free and avoid hypoglycemic reactions. She now weighs 94 lbs.; in a little over two years she has more than doubled her weight. She is able to take strenuous exercise. She rides horseback three mornings a week for 2 hours, and she swims for 2 hours the other 3 mornings, and she is going to school. Aside from the fact that she has to weigh her food and has to take the injections, she feels and acts as any normal healthy child would. She has gained 1¼ inches in height, but her great general improvement is due to the fact that her muscles have increased in tone and strength and that she is able to stand in a more erect position.

This case illustrates the results that we may obtain even at this time under the most favorable conditions by the careful administration

of insulin. Some patients show much more marked clinical improvement with regard to their subjective symptoms. We have had some pessimistic patients who were at the point of giving up, who have had their whole outlook on life changed and who welcome their injections and the increased diet.

There are several complications in diabetes, the greatest of which is coma. We have now had about 15 cases of coma and have had some splendid results in the treatment of some of them. Not all of the patients recover, because when a patient is in coma for a considerable length of time, for 10 or 15 hours, he is more difficult to manage. One patient who had been in coma for 24 hours, although she was rendered sugar-free and acetone-free, did not recover. The blood pressure remained very low, and she finally died. Necropsy was performed soon after death, and the liver was found to contain glycogen. The blood sugar was at almost normal level, and the urine was acetone-free, showing that she did not die from coma. Another patient died of pneumonia. One patient was in coma for about 24 hours or a little longer and was very slow in rallying; before treatment could be properly instituted she died. Another patient died of severe septic gangrene after refusing to have the limb amputated. This patient was sugar-free and acetone-free at the time of death. We have had seven patients with severe coma recover. By coma we mean a degree of surgical anesthesia. I can possibly best illustrate this in more detail by reporting the case of a child, 12 years of age, admitted to the Hospital for Sick Children on September 13 of last year. Sugar had first been discovered in the urine the previous April. She had been placed on a diet, but she did not adhere to the diet and became more and more rebellious until just previous to admission she consumed a large number of grapes and superimposed on that a number of olives. She developed pain in the stomach, headache, vomiting, became drowsy and finally went into coma. On admission the blood sugar was 0.5% per 100 mg., and she had a marked odor of acetone on the breath. The air hunger was marked. She had all the typical signs of coma. One hour after admission she was given 4 c c. of insulin. The blood sugar taken 2 hours after the initial dose showed that it was reduced from 0.5 to 0.2%. There had been a 4 + Rothera test for acetone in the urine. This was reduced to 2 + in about 4 hours after the initial injection. The blood sugar went down to 0.1%. We then began to fear that she had received an overdose and had hypoglycemia, and we

administered sugar intravenously. Despite the intravenous injection of 1,700 gm. of glucose, the blood sugar went down to 0.08%. The urine was almost acetone-free; it just showed a faint transitory trace to the Rothera test. At this stage—she had been sugar-free for 4 or 5 hours while receiving the treatment—the whole clinical picture changed. She came out of coma and became restless, tossing about in bed and using incoherent language; she appeared toxic, her eyelids were heavy and closed, the pulse increased in rate. The temperature at the same time became rapidly elevated from 101 to 105, and the pulse became rapid, going up to 140 +. Respirations were increased, and with the tossing about in bed she used up a great deal of energy and finally became very weak. The temperature went up to 106.2 F., and there did not seem to be much hope. This was about 24 to 36 hours after admission. A few hours after admission we gave her an enema, which was not thoroughly evacuated. About 12 hours after admission, the enema was repeated without good effect. We then repeated the enema every 2 hours in the endeavor to get rid of the possibly intestinal toxemia, because on repeated examination of the chest it was found to be normal. It seemed most likely that she was suffering from intestinal intoxication. Following these series of enemas the temperature began to fall, and about 6 o'clock on the second morning after admission the child passed a large amount of putrefying, foul-smelling fecal matter, and from that time on made an uninterrupted recovery. On the 6th day after admission she was placed on a diet of 20 gm. of carbohydrate—I have forgotten how much fat and protein—on a diet with a total value of 420 calories and with sufficient insulin to render her sugar-free. The diet was gradually increased, and after about one week it was found that less insulin was necessary to render her sugar-free in spite of the fact that the diet had been increased from 420 to 800 calories. The insulin treatment was continued until October 13, that is, exactly one month from the date of admission. By this time the diet had been increased to 1,400 calories, 76 of which were derived from glucose. The administration of insulin was then discontinued entirely, and the diet reduced to 420 calories, which she had received on the sixth day after admission. The diet was then increased every other day, and she was without insulin, until on November 13, 2 months after admission, she was taking 1,470 calories, about 80 gm. of which were carbohydrates; she had remained sugar-free since the 6th day after admission. In other words, after

one month's treatment her tolerance was raised from 420 to 1,470 calories, without showing sugar in the urine. From this one would conclude that there is a definite increase in toleration following the administration of insulin, but this same thing could be accomplished with diet alone if the case had not been such a severe one of coma and acidosis preceded by intestinal intoxication. Furthermore, this case is only of six months' duration, and the patient had a great deal of natural power from her own pancreas. The value of insulin treatment in that case was considered to be chiefly in combating the complications.

Other complications can be met in the same fashion. In severe cases of gangrene operation should be performed and the patient can be rendered sugar-free and acetone-free, with normal blood sugar, and can be balanced on a subsequent diet to enable him to stand even a major operation, such as amputation of a leg. We have had one case complicated with early pulmonary tuberculosis, but the pulmonary tuberculosis had not advanced to the stage when one would expect a rapid decrease in the patient's strength and vitality and resistance to combat the tuberculous infection. Similarly, more minor cases have been overcome. We have maintained some of our severe diabetic patients sugar-free and acetone-free through tonsillectomy, extraction of teeth and operations of that nature. The general results have been satisfactory, and it is gratifying that the work has progressed so rapidly. The greatest reason for this has been the wholehearted cooperation that we have had from so many interested investigators. Early in the management of the research the University of Toronto appointed an Insulin Committee the members of which formulated a program; Professor MacLeod is the one to whom the greatest credit is due for the success of the work. We manufacture insulin at the school, and we supply it in as large quantities as possible for the use of the various clinics in this country and in our own country. The Eli Lilly Company of Indianapolis has done excellent work in production, and to Dr. Clowes and Dr. Walters is due great credit for their untiring efforts in this direction. In that way a great deal of commercial exploitation was prevented. The Eli Lilly Company supplies what they call "iletin" but we hope in the scientific literature it will go under the name of insulin. The insulin was sent to the various diabetic clinics for control and for research work, and the rapidity with which the work has been done is, as I said before, for the greatest

part due to the combined efforts, teamwork and cooperation that the Toronto group has had from these investigators. However, the greatest satisfaction of all we get from patients who have received the treatment, and this gratification is most stimulating and inspiring not only to our own group, but to all of those who are treating patients. There are a great number of problems with which we have to deal; for instance, whether it is better to maintain a patient sugar-free and to risk hypoglycemic reactions or to give them a much increased diet and insulin and allow them to keep on excreting sugar. We have had patients who have done remarkably well and gained in weight and strength after this treatment. There are a great number of problems in connection with the underlying principles of metabolism, but these problems can be settled at a future date when it is not so important to adapt the treatment to the greatest number of patients.

Again on behalf of the Toronto group we would like to express our thanks to the various diabetic centers and clinics in the United States who have cooperated so marvelously in this research.

DISCUSSION

DR. R. T. WOODYATT: At this late hour I will not detain you by attempting to add to what has already been said by the discoverers and developers of this important adjunct in the treatment of diabetes.

People have suffered from diabetes from time immemorial. There have been mild cases in patients who undoubtedly lived their full expectancy of life with more or less annoyance, and there have been more severe cases with life expectancy diminished, and in others physical impairment and sudden death have ensued. More than a century ago diabetes came under dietetic control as a result of the work of Rowland. By regulation of diet, it is possible to keep patients alive and working for many years. It has been possible to bring the tolerance up to certain limits as a result of diet, but it has not been possible until recently to raise the tolerance above the natural level to which it could be raised by the most strict dietetic and hygienic circumstances. During the last year and a half there has come into existence a new material by which it is possible to create a new tolerance immediately. This result was accomplished by Dr. Banting and carried out by the Toronto group. I know every one here like myself have nothing but admiration for this group for this important scientific advance.

DR. RUSSELL WILDER, Rochester, Minn.: I want to express my appreciation of the opportunity to take part in this discussion. I think we all agree that this discovery represents the greatest advance that has been made in the field of physiology or medicine in a good many years. The discovery of insulin is acknowledged to be one of the greatest advances of modern medicine, if it does not surpass all other preparations in use, not excluding arsphenamin or diphtheria antitoxin.

At the Mayo Clinic we are indebted to the Toronto group for the privilege of taking part in the clinical investigations with this interesting material. The

results have been satisfactory. Some remarkable results, similar to those described by Dr. Banting, have been obtained with patients in coma. Working in our laboratory now is a young man who was in an extreme state when he arrived, and in 36 hours with insulin and glucose he was serologically and symptomatically practically normal. More significant than this, as Dr. Woodyatt has pointed out, is the effect that can be obtained by judicious administration of insulin and a judiciously controlled diet to enable the patient who has lost tolerance to regain weight and strength so as to become, barring the necessity of continued use of insulin, practically normal.

It is worthy of notice for the benefit of those whose sympathies are limited to the lower animals that this discovery, as Professor MacLeod has pointed out elsewhere, is due to experiments on dogs. It is inconceivable that this advance could have been made without the use of animal experiments.

EPIDEMIOLOGY OF BOTULISM

J. C. Geiger
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March 24, 1922

Impressed by the grave responsibility thrust on the canning industry of this country incidental to the tragic botulism outbreaks which followed the consumption of factory preserved ripe olives, the National Canners Association, the Canners League of California and the California Olive Association proposed in December, 1919, a detailed investigation in order to determine the danger from botulism, how it arises and how it can best be avoided and overcome. Through the instrumentality of these associations, funds were provided to support research work on certain definite phases of botulism in the United States. It was decided to form a commission in California, consisting of a research worker from the United States Public Health Service, the California State Board of Health, Stanford University and the University of California. The commission was composed of the following members: J. C. Geiger, epidemiologist of the United States Public Health Service; E. C. Dickson, associate professor of medicine in the Stanford University Medical School; and K. F. Meyer, professor of research medicine and acting director of the George Williams Hooper Foundation for Medical Research, representing the University of California, and, as consulting bacteriologist, the California State Board of Health.

It was decided that the investigation should be conducted in three directions: first, a careful statistical analysis of the anatomic and bacteriologic data which were already available or which could be collected from previous outbreaks of human and animal botulism; second, a clinical study of typical and atypical cases, with special emphasis on the value of the specific serum treatment; and third, an extensive experimental study dealing with the distribution and sources of B. botulinus, including particularly an investigation of the factors predisposing to the production of toxin in certain types of food. The original plans to confine the study to botulism in the State of California were subsequently broadened, and this report includes a study of all the outbreaks in the United States concerning which records were available.

Following are the conclusions of this investigation:

(1) Outbreaks of botulism in the United States, following the consumption of toxin-containing food products are not infrequqent, but as a cause of death this intoxication is by no means as important as the numerous publications in the medical journals would imply.

A total of 91 reports dealing with single or group outbreaks of botulism have been collected by the Commission. In 30 instances only has the clinical or the postmortem diagnosis been confirmed by toxicologic tests. The following food products have been proved or assigned as the causes for the intoxications:

Home preserved products: 51 outbreaks, 16 proved.

Home canned string beans: 17 instances, 4 proved (food spoiled and bad odor 7, bad taste 4, no signs of spoilage 3, unknown 3 outbreaks).

Home canned corn: 9 instances, 4 proved (spoiled and bad odor 6, taste 2, not known 1 outbreak).

Home canned asparagus: 5 instances, 3 proved (spoiled and bad odor, taste 1, no signs of spoilage 1 outbreak).

Home canned apricots: 3 instances, 1 proved (spoiled 1, bad taste 2).

Home canned pears: 2 instances, none proved (spoiled 1, bad taste 2).

Home canned spinach: 2 instances, none proved (spoiled 1, no signs of spoilage 1).

Home canned beets: 1 instance, none proved (no signs of spoilage).

The deduction drawn from Report 90 and 91 are included.

Homebrew liquor made from spoiled home canned fruits and vegetables: 1 instance, not proved.

Cottage cheese: 2 instances, 1 proved (putrefactive odor 1, spoilage unknown 1).

Home pickeled mackerel and herring: 1 indirectly proved, (spoiled).

Home cured ham: 2 instances, 1 proved (not spoiled 1, unknown 1).

Blood sausage: 1 instance, proved (spoilage unknown).

Salted pork: 1 instance, not proved (spoilage unknown).

Beef products: 3 instances, inconclusive, not proved (spoiled 1, not spoiled 1, spoilage unknown 1).

Minced chicken: 1 instance, inconclusive.

Commercially Preserved and Canned Products—Thirty-one outbreaks, 14 proved.

Commercially canned underprocessed spinach: 6 instances, 5 proved (2 visibly spoiled and odor, no signs of spoilage 4).

Commercially packed minced olive relish: 3 instances, 1 proved, 2 indirect (1 bad odor, 2 no signs of spoilage).

Commercially pickled and bottled ripe olives: 7 instances, 6 proved, 1 not proved (4 visible spoilage, 1 bad taste, 1 no signs of spoilage, 1 unknown).

Commercially canned beets: 2 instances, none proved, 1 indirectly (1 bad taste, 1 no signs of spoilage).

Commercially canned string beans: 3 instances, none proved, 1 inconclusive (1 spoiled, 2 unknown).

Commercially canned corn: 1 instance, not proved (1 bad taste).

Commercially packed tomato catsup: 1 instance, not proved, (unknown).

Commercially canned pork and beans: 1 instance, inconclusive, (spoiled).

Commercially prepared sausages: 2 instances, inconclusive, not proved (no sign of spoilage).

Commercially prepared ham: 1 instance, not proved (bad taste).

Commercially bottled clams: 2 instances, not proved (unknown).

Commercially canned tuna fish: 1 instance, not proved (spoiled).

Evaporated milk: 1 instance, not proved (spoiled).

In recent years a striking increase of botulism has taken place in various localities, and foodstuffs which were considered safe from B. botulinus deterioration have been found to be the cause of this type of poisoning. Laboratory studies have also demonstrated that B. botulinus is more widely disseminated in nature than has been generally suspected. Botulism cannot be considered primarily a problem of California, the Pacific Coast States or the Western slope of the Sierra Nevada and Rocky Mountains. The organized work in California enabled the Commission to investigate sources of information which were not accessible in other states. It is not unlikely that some of the essential findings determined for the Pacific Coast could be duplicated by the activities of a similar Commission in other localities.

(2) Since 1889 a total of 45 instances of human botulism have been reported for the State of California. A total of 132 people with 81 deaths are involved in these observations.

(3) There is no evidence of any special incidence at any age period. The sex distribution for 115 cases can be summarized in the following formula:

Children: Males: Females: 1: 3:13: 3:46

(4) The intoxication rate is very high; as a rule, all who ate the poisonous food became ill. The available data do not permit a comparison of the infectivity rate of food poisoning with the intoxication rate of botulism. The number of fatal cases varies greatly in different outbreaks. The case mortality rate for 129 cases in California is 61.3%. For the children, the mortality rate is higher than in adults.

(5) More than one half of all the botulism outbreaks of California have occurred during the fall and winter months, namely, between October and February. In contrast with the bacterial food infections which are usually prevalent during the hotter months, botulism bears no relation to the climate, because it is as a rule intimately connected with the consumption of preserved food which takes place during the winter season.

(6) Twenty-eight, or 62.3%, of the outbreaks in California were caused by plant food products, while 11 or 24.4% were attributed to animal food products; in 6, or 13.3%, of the outbreaks the carriers of the toxin were unknown; 13 outbreaks or single cases were caused by home canned string beans, 2 by commercially packed spinach, 1 by commercially pickled ripe olives, and 3 by commercially prepared minced olive relish, 3 by home canned apricots, 2 by home canned pears, 1 by home canned asparagus, 1 by homebrew liquor, one by home canned and 1 by commercially canned corn, 3 by home preserved beef products, 1 by commercially preserved and 1 by home preserved pork products, 2 by commercially bottled clams, 1 by commercially packed pork and beans, 1 by commercially packed tuna fish, 1 by home pickled mackerel and herring, and one by cottage cheese. In 12 instances, commercially packed, and in 27 observations, home canned products were involved.

(7) The prevalent idea that the food must always be visibly spoiled in order to be toxic is not entirely supported by the available observations, although there is no doubt that 5 single or group outbreaks were caused by home canned string beans which were spoiled by appearance, odor or taste. The home canned apricots and pears responsible for outbreaks were either moldy or visibly spoiled, and had a sharp bitter taste. In 2 instances, the home canned corn and asparagus were distinctly spoiled and emanated an offensive odor. In 1 report dealing with home canned corn, it is mentioned that the product was not spoiled

but tasted "metallic". It is definitely stated that 2 jars of home canned string beans responsible for 2 outbreaks showed no evidence of spoilage either by odor or taste.

Commercially packed spinach was spoiled in one and appeared normal in taste and odor in another outbreak. The commercially canned minced olives connected with 2 single or group outbreaks were bitter in taste and on standing emanated a definite odor. No signs of spoilage was noted in 1 can of the same product, although it contained toxin. In the majority of instances, the canned food was so spoiled as to attract the attention of the one who opened the container, but it should be emphasized that in 4 instances (home canned string beans, commercially packed spinach and minced olives) macroscopic spoilage in form of abnormal consistency or appearance was not visible. B. botulinus spoilage can therefore not always be determined by the appearance or odor of the food.

(8) The frequent occurrence of botulism in the southern section of California is closely connected with the distribution of B. botulinus spores in nature, particularly in the soil.

(9) An investigation in the state of Washington revealed 13 outbreaks of human botulism (inclusive report 90 and 91). A total of 26 people, with 18 deaths, are involved in these observations. A careful survey in the Yakima Valley demonstrated that there have occurred in this locality during the last 5 years, 8 outbreaks of human botulism, 27 outbreaks in domestic fowls, 26 in horses, 3 among cattle and one among hogs. The mortality rate among the human cases was 69.1% Aside from being an important public health problem, botulism assumes in the Yakima Valley also an economic aspect. Home canned corn, home canned asparagus and home canned spinach were the foods responsible for botulism. A single case possibly due to commercially canned evaporated milk has been investigated.

(10) Since 1912, a total of 33 instances of human botulism have been reported for the entire United States and Canada, exclusive of the states of California and Washington. A total of 187 people, with 114 deaths, are involved in these observations. The case mortality rate is 60.9%. Twenty-four, or 72.4%, of the outbreaks were caused by plant, while 7, or 27.3% were attributed to animal products. In 16 instances commercially preserved foods were involved, namely pickled ripe olives, 6 (all proved), spinach 4 (3 proved), strong beans 2 (not proved),

beets 2 (one proved indirectly), tomato catsup 1, and sausage 1 (inconclusive). The following home preserved foods are mentioned in the reports: string beans 4 (1 proved), corn 3 (1 proved), asparagus 1 (proved), beets 1 (not proved), cured ham 3 (1 proved), blood sausage 1 (proved), cottage cheese 1 (proved), and minced chicken 1 (not proved). The commercially preserved foods originated in the following states: California (9, pickled ripe olives and spinach), Kansas (1, string beans), Ohio (1, beets), Wisconsin (1, sausages). In the majority of the reports it is stated that the canned food was visibly spoiled either in appearance or in odor. Canned spinach and home or commercially preserved beets may show little spoilage, although they may contain a potent toxin. The causative foods were either improperly preserved or underprocessed (ripe olives and 2 packs of commercially canned spinach, home canned string beans, corn and asparagus).

(11) Botulism is not uncommon among barnyard fowls in urban and rural poultry flocks. One hundred six observations indicate that spoiled home canned plant products, such as string beans, corn, asparagus, peas, spinach, apricots and fish, are primarily responsible for the intoxications. The diagnosis has been supported by bacteriologic examinations in 25 instances. In 3 cadavers of chickens obtained from 4 different outbreaks, the presence of B. botulinus toxin was demonstrated by the inoculation of guinea-pigs with the filtered saline extract of the crop content. B. botulinus, type B, was found in 4 outbreaks, either in the causative food or in the crop of the chickens.

(12) Certain forms of "foreign poisoning" in horses are probably true equine botulism. Preserved spoiled vegetables or ensilage caused 4 different outbreaks; the presence of B. botulinus and its toxin was proved indirectly by immunization experiments or by the coincident occurrence of botulism in human beings or fowls. Until experimental studies have demonstrated the presence of the preformed B. botulinus toxin in the suspected feed, the numerous isolations of this organism from the cadavers of horses or the suspected wholesome or spoiled feed possess no diagnostic significance for equine botulism. This statement applies in particular to those cases of "forage poisoning" in which feed, moldy hay, corn, potatoes, etc., are suspected as being causative.

(13) B. botulinus is in certain localities an inhabitant of the intestinal tract of cattle. In the course or during the agonal stage of some diseases, it may invade the tissues. These bacteria have probably no

etiologic relationship to the lesions or to the diseases from which they have been isolated. The occurrence of spontaneous botulism in cattle has not been proved.

(14) Botulism in hogs, dogs, cats and goats is rare, and has been noted following the ingestion of poisonous home canned string beans, peas and possibly pears.

(15) A typical case of human botulism is usually characterized by delayed onset, with or without initial acute gastro-intestinal disturbance, marked general muscular weakness, disturbances of vision with diplopia and blepharoptosis, dryness of the mouth and pharynx, accumulations of thick mucous in the pharynx, loss of ability to swallow and talk, strangling spells and regurgitation of fluids through the nose on attempts to swallow and persistent constipation. There is rarely any pain or disturbance of sensation. Mentality remains clear, the pulse rate steadily increases as the intoxication progresses, and the temperature is usually subnormal.

Death usually results from respiratory failure, but insufflation pneumonia is not an uncommon cause.

(16) The gross appearance of the tissues at necropsy presents nothing that is characteristic. There is marked congestion of all viscera, and there may be hemorrhages. Microscopic examination usually reveals cellular thrombi in the blood vessels. Perivascular lymphocytic infiltration is not found.

(17) There are no data to prove or disprove the efficacy of botulinus antitoxin as a prophylactic or therapeutic agent. In all recorded cases, when homologous antitoxin has been administered it has been given too late in the course of the intoxication to be of any value.

(18) The diagnosis of botulism was in 11 outbreaks established by the demonstration of the toxin of B. botulinus in the remnants of the causative food. These tests have been thorough in the recent outbreaks caused by ripe olives and spinach. In 6 instances, the food was not tested for toxin, but B. botulinus was isolated in shake or enrichment cultures; in 3 outbreaks, the bacteriologic diagnosis was made from jars of home canned vegetables of the same lot that had caused the poisoning.

In 8 single or group outbreaks, the remnants of the suspected food were not available, and the diagnosis was made indirectly; namely, B. botulinus was isolated in 5 instances from the crop or gizzard of

poisoned chickens, in 2 observations from the stools of clinical cases and in 1 outbreak from the jejunal walls of a fatal case.

(19) Only 30 outbreaks, or 32.9%, of the available observations have been proved bacteriologically. B. botulinus, type A, has been identified in 21, while type B has been found in 3 outbreaks.

(20) The epidemiologic data indicate that a true botulism infection following the ingestion of toxin-free spores never occurs in human beings. In 4 instances, it was proved that the eating of uncooked spoiled food caused botulism, while the ingestion of portions of the same food after cooking provoked no symptoms. Canned goods deemed to be abnormal either by appearance of the container or by the odor should be destroyed, not heated and eaten.

(21) Spoilage of home or commercially canned food products due to B. botulinus represents an insignificant part of the yearly pack. It is the result of inadequate sterilization. The usual methods of processing must be systematically studied, and the packer should aim at absolute sterility of the food products whenever it is possible.

Spoilage due to B. botulinus has been limited to a few definite varieties of plant products, such as home canned string beans, corn, asparagus and spinach, also home canned beets, apricots and pears, and commercially pickled ripe olives, commercially packed spinach, string beans, beets and corn. B. botulinus spoilage in ordinary commercially packed fruits and such vegetables as tomatoes has not been mentioned in the reports. Furthermore, many vegetables such as corn and peas require such rich processes to destroy the nontoxic thermophilic spoilage organisms found in them that the occurrence of botulism from them is improbable.

(22) In the United States, preserved plant products are primarily involved in botulism outbreaks, while in Germany pork and fish products contain the fatal poison. In both countries, botulism is caused by the use of preserved foods which are not thoroughly cooked before they are eaten.

SOME STAGES IN THE DEVELOPMENT OF THE CRANIAL GANGLIONS IN MAN

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April 27, 1923

The many primitive features which appear in the early development of man support the conclusion that man, like other primates, is in most respects a primitively organized mammal. During recent years a series of young human embryos has become available, thanks to the more general interest and help from the surgeons and the cooperation of those anatomic laboratories which possess such rare material, so that we can at least decipher the broad outlines of the early development of man. The forebrain, midbrain and hindbrain can be positively identified before the neural folds have begun to close, and from then until the seventh week after fertilization the hindbrain is the dominant feature of the nervous system as it is in other vertebrates. The data we have concerning the development of the cranial ganglions can be interpreted in the light of comparative and experimental embryology, although the series is still incomplete for such studies. Cells from two distinct sources enter into the formation of these ganglions; as in the lower vertebrates, some come from the central nervous system (neural crest), others from thickenings of the ectoderm called placodes. Both neural crest and placodes of the 5th, 7th, 9th and 10th nerves are definitely related to the visceral elements of the head and neck, namely, the branchial arches and the intervening gill pouches. The sequence of events is briefly as follows: In an embryo with 2 pairs of mesodermic somites (about 1.5 mm. long and 18 days old), there is an ectodermal thickening roughly outlining the cutaneous area subsequently innervated by the trigeminal nerve. The first gill pouch (which will become the tympanic cavity and Eustachian tube), separates it from a similar thickening corresponding to the hyoid arch. In embryos with 7 to 8 pairs of somites, cells arise from the neural folds and migrate toward the ectodermal thickenings, fusing with them in 13 to 14 somite stages. Cells from both sources contribute to the formation of the ganglions, which begin to take form in 23 somite stages (about 25 days old). In addition, many of the neural crest cells develop into supporting elements of the visceral arches and the maxilla.

TOXICITY OF COCAIN AS A LOCAL ANESTHETIC

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April 27, 1923

We know that cocain is toxic and that persons differ widely in their susceptibility to this drug. Many deaths have resulted from its use. The mild toxic symptoms that appear while cocain is being used as a local anesthetic are well known.

For many years cocain has not been used without epinephrin. Therefore it has always been a question whether the toxic symptoms were due to cocain alone or to cocain strengthened by epinephrin, or to epinephrin, or to epinephrin reinforced by cocain. Some of the best authorities consider that epinephrin reduces the toxicity of cocain. It is common practice to inject epinephrin after collapse resulting from cocain.

From animal experiments on another problem the suspicion arose that epinephrin increased the toxicity of cocain. By injecting weak cocain solutions into the veins of animals at a slow and uniform rate with the Woodyatt machine, we were able to get the minimum lethal dose of cocain as influenced by epinephrin. The results led us to conclude that the addition of 1, 5 or 10% of epinephrin (1:1,000) increased the toxicity of cocain 47, 95 or 140%.

Using the same method of injection, we determined the variation in the minimum fatal dose of cocain as influenced by rate of introduction into the blood stream. The small variation in the size of the minimum fatal dose led us to conclude that the rate of absorption of cocain has practically no effect on the killing dose.

The mechanism of the temporary toxic disturbance encountered so frequently was investigated. Arterial and intracranial venous blood pressures were taken after submucous injections of epinephrin, cocain and cocain with epinephrin. These led us to conclude that the great synergistic action of cocain and epinephrin on the circulatory system produced intracranial venous congestion. The intracranial venous pressure rise expressed in percentage of normal was about twice as great as arterial pressure increase expressed in the same way. The resulting asphyxia of the central nervous system is capable of producing all of the disturbances commonly encountered. By swabbing the throat

with 20% cocain, sufficient is absorbed immediately to exert exceedingly strong synergistic action with epinephrin injected submucously.

A series of observations on blood pressure was made on persons undergoing tonsil operations. Cocain was swabbed on the throat, and epinephrin with procain was injected. In all cases there was a rise of blood pressure varying from 20 to 114 mm. of mercury. The average rise was 41 mm. of mercury, or 34.2%. Those patients that suffered toxic symptoms had an average rise of blood pressure of 66 mm. of mercury, or 51.5%.

THE FOOD METABOLISM OF OBESITY (*Abstract*)

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April 27, 1923.

Obesity must be differentiated from what may be called physiologic overweight. By physiologic overweight we mean an increase in weight due to increased food intake, lessened energy expense or both. This is a common experience. It is generally considered that the same two factors are predominant in the etiology of cases of obesity other than those associated with endocrine disturbances. Careful study of cases of obesity must force us to the conclusion that practically all such cases are dependent at least in part on factors other than a mere disproportion between calories taken in and calories expended. Of the many persons of sedentary lives and occupations who overeat, only the occasional one develops obesity. On the other hand, there are thin, healthy persons whose habits show no disproportion between caloric intake and expense. We have some controlled dietary studies to prove that there are persons showing no dependence between weight and caloric balance.

Some of these persons show signs of endocrine disturbances, the myxedema of the subthyroid and the adiposity syndrome of pituitary disease being the most striking examples. Yet even in cases with definite clinical manifestations of endocrine disturbance, with the exception of myxedema, the underlying metabolic disturbance remains obscure. In myxedema and perhaps in some pituitary disturbances, a lowered basal metabolic rate has been reported; in other cases of obesity, the metabolic rate has been normal and has thrown no light on the subject. To label a case an endocrine case does not explain the fundamental metabolic disturbances producing obesity.

We undertook a study of the actual use of food by persons of unusual weight. Believing that a lack of balance between caloric intake and expense does not by itself cause obesity, it seems plausible to postulate a different metabolic mechanism in obese and in thin persons. The relation of obesity to diabetes mellitus has for years received attention; recently renewed interest in this correlation has led some students to consider obesity as a prediabetic condition. It was hoped

that our studies on obesity might throw some light on the early metabolic changes in diabetes.

METHOD

In our first experiments, we studied with the Benedict portable calorimeter a series of normal persons of both sexes, several unusually thin men and women remaining obese on subcaloric diets.[1] The regulation procedure for basal metabolism was adopted, and immediately after the basal determination a meal consisting of 100 gm. of saccharose and the juice of one lemon in water up to 300 c.c. (equal to 408 calories) was given. The oxygen consumption was measured every half hour until the basal level was again reached. The increment in metabolism from the food ingestion is then easily measured. As a convenient method of presenting results the increment is expressed as percentage increase over the basal for each period of observation.

The results of this first study were inconclusive. Taking each subject individually and comparing the known obese with the normal and with the unusually thin, no specific type of reaction was apparent for either group. Averaging all cases on a simple although artificial rule of normality, namely, that the height in centimeters is 100 plus the weight in kilograms, resulted in a suggestion of variation. The curve plotted for each half hour suggests that in the obese the increase in metabolism from 408 carbohydrate calories is definitely less than in the normal or thin group.

The second phase of the work consists of repeating the saccharose experiments, using the Tissot open circuit method and studying also the nitrogen excretion. The results of this work are interesting and suggest a new conception of the metabolism of obese persons. The percentage of total calories burned in each period which are derived from protein does not vary greatly in the fat, thin or normal group. The percentage of total calories derived from fat and carbohydrate shows a definite difference between the fat and the thin group. Fat persons do not burn their fat to the same extent as normal persons; likewise, fat persons burn their carbohydrates to a much greater extent than do thin ones.

The last phase we are able to report at present deals with protein meals. It is interesting to note that the obese persons took the meal

[1] Part of this phase of the work was done in the laboratory of the department of home economics at the University of Chicago, with the guidance of Professor Katherine Blunt.

with difficulty, eating slowly, and in 2 instances suffering from nausea. The results of this study show no variations in total increase in metabolism in 3 groups. Practically the same differences in the utilization of fat and carbohydrate by the 2 groups was seen after the protein meals as has been noted after the saccharose.

SUMMARY

The study suggests the following conclusions:

The total increase in metabolism after a carbohydrate meal seems to be less in the obese than in the normal or pathologically thin person.

After a protein meal this variation is not seen.

After both types of meal a difference is seen in the proportion of foodstuffs metabolized. The obese person burns less fat and more carbohydrates than the normal.

The total study seems to point to a metabolic mechanism in the obese in which fats are not burned, a mechanism perhaps similar to that seen in the sugar burning metabolism of diabetes.

Further studies are in progress.

ETHYLENE AS A GAS ANESTHETIC

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April 27, 1923

In our first communication [1] we published results showing that ethylene gas in proper concentration and admixture with oxygen possessed marked analgesic and anesthetic properties when administered to the usual laboratory animals. We likewise published results showing that man was as susceptible to its influence as the laboratory animals. On the subjective side it was readily established that analgesia and surgical anesthesia are induced very rapidly "without any sense of asphyxia, but, on the contrary, with a sense of well-being and comfort"; and that, on recovery, which is very rapid, many volunteers experienced only a very temporary nausea, others experiencing no ill effects whatsoever, except for a slight and temporary sense of weakness even under conditions which are known to favor untoward effects.

These preliminary experiments were performed on normal, healthy men. Further extension of the work demanded actual operative work in a hospital and on patients requiring surgical interference; for we had gone as far as it was possible to go in a physiologic laboratory.

We therefore arranged for a further demonstration on ourselves of the anesthetic properties of a suitable ethylene-oxygen mixture before a group of surgeons, physicians and professional anesthetists, Dr. Carl Dragstedt administering the gas.[2] Within several days after this demonstration (March 14, 1923), surgical work with its use was begun at the Presbyterian Hospital, Chicago. All precautions were taken to give the gas a fair but adequate trial. After it had been used in simple and uncomplicated cases with gratifying results, more extensive and prolonged operations were undertaken with similar success. Impressed with its many desirable properties, other staff surgeons at the hospital began to use it. From March 14 to April 26, 106 operations were performed.

[1] Luckhardt, A. B., and Carter, J. B.: J. A. M. A., 1923, 80, p. 765.

[2] There were present, at this demonstration, Drs. Lester R. Dragstedt, A. D. Bevan, Dean Lewis, Gatewood, H. L. Jones, G. Hovnanian, A. E. Kanter, Isabella Herb, Mary Lyons and Frances Haines.

CLINICAL ASPECT OF THE WORK

We offer a brief analysis of the clinical aspect of the work in the form of a short report, which we recognize as quite superficial and incomplete.

Sex.—Of the 106 patients operated on, 42 were males and 64 were females.

Age.—The average age of the patients was 39.8 years. The youngest patient was a boy, aged 10; the oldest, a man, aged 64.

Nature of Operations.—We have grouped the operations as occurring on the head, thorax, abdomen, perineum or extremities. In addition, ethylene has had some use in obstetrics. This is a highly arbitrary system of grouping and not above criticism. It allows, however, of a rapid enumeration of the various operations that have been performed:

(*a*) Head: Removal of a wen; excision of a carbuncle; abscess of the jaw; mastoid operation; removal of tonsils; osteomyelitis of jaw with removal of sequestrum; opening of abscesses of neck and in axilla; drainage of cervical abscess.

(*b*) Thorax: Two excisions of breast tumors; two radical breast removals.

(*c*) Abdomen: Six herniotomies (one double); 3 exploratory laparotomies; 6 appendectomies; operation for undescended testicle; a cystostomy; cholecystectomy; 2 operations for shortening the round ligament of the uterus.

(*d*) Extremities: Reduction of a dislocated shoulder; 5 operations consisting of the amputation of a toe; operation on fractured and dislocated ankle; manipulation of shoulder for breaking up of adhesions; aspiration of a knee joint; osteomyelitis of tibia; osteomyelitis of femur (3 operations); stretching of the sciatic nerve; bilateral amputation of thighs; osteomyelitis of ileum; removal of a sequestrum from the tibia; 2 operations for bunions; 2 operations on varicose veins; an astragalectomy; operation on a double fracture of the leg and dislocation at ankle of 6 months' duration.

(*e*) Obstetrics: Ethylene was used in 4 normal deliveries with very satisfactory results. It was found better than nitrous oxid used the preceding hour or hours. An 80% concentration was employed. The color of the patient remained good. The fetal heart tones remained unchanged.

(*f*) Perineum: Dilatation of cervix and curettage (9); 2 radium needles into cervix uteri; pelvic examination; double rectal fistula; 2 prostatectomies; 2 operations for removal of hemorrhoids; cystoscopy; 5 operations in which radium needles were introduced into the prostate; ureteral catheterization; anal fissure; vaginal cesarean section; perineal incision prior to delivery and subsequent repair; insertion of Voorhees bag; amputation of cervix uteri; perineorrhaphy; manual exploration of uterus; incision of pelvic abscess; colpotomy.

Concentration of Ethylene Used.—The average concentration of ethylene used in 101 operations (in which a record was kept) was 81.9%, the other gas, as with nitrous oxid administration, being oxygen. Individual variation exists as with other anesthetics, regardless of the nature of the operation. Whereas a 77 to 80% ethylene and a 23 to 20% oxygen mixture sufficed to render some patients analgesic or even anesthetic, others were not in a state of surgical anesthesia unless the ethylene was given in a concentration of 90 or even 95%. The latter patients were exceptionally resistant and were few in number. Otherwise the percentage of ethylene necessary for the 101 patients as a whole would not average down to 81.9% ethylene. Such a concentration allows, as will be noted, of the simultaneous administration of about 18% oxygen.

Duration of the Operations.—The length of the operations varied considerably—from a few minutes to 1 hour and 50 minutes. The average length of 92 operations was 27.8 minutes.

Recovery from the Anesthetic.—In the entire series of 92 cases in which ethylene was the sole anesthetic used, we find no record that the patient had not recovered his senses within 5 minutes after discontinuance of the anesthetic. Following the shorter operations, recovery was almost immediate. But even after very long operations the patients were usually quite rational within 3 minutes after ceasing to breathe the ethylene-oxygen mixture.

Nausea and Vomiting.—Three of the 92 patients felt nauseated, and 14 vomited. The retching or vomiting was of short duration, occurring when the patient was but lightly anesthetized or for a very brief time immediately on recovery from the anesthetic. It consisted very often of a few retching movements and was never serious.

Evaluation by the Surgeon.—Nineteen surgeons operating with ethylene as the anesthetic agent have made this preliminary study

possible.[3] Their verdict was not only that the gas was "good" or "very satisfactory," but that it produced in a given type of operation or manipulation a decidedly better relaxation than was possible with nitrous oxid. Upper or lower respiratory infections were not brought on by its administration, nor were such, when existant at the time of operation, made worse.

Opinion of the Anesthetists.—The administration of ethylene was almost exclusively in the hands of Drs. Isabella Herb and Mary Lyons. Whether used to induce anesthesia in an ethylene-ether sequence (14 cases) or as the sole anesthetic agent, these well-known anesthetists felt very well satisfied with it, as the following quotations, culled from the protocols of various patients, will prove:

Unable to hold under nitrous oxid in similar operation. Better relaxation than with nitrous oxid. (Herb.)
Sequence easier than with nitrous oxid. (Herb.)
Much better than nitrous oxid. Patient given nitrous oxid several times before—always unsatisfactory. (Herb.)
Have given him six anesthesias before, always with excitement. None this time. (Herb.)
Quieter induction. (Lyons.)
Very satisfactory. (Lyons.)
Patient with hemoglobin of 35%. This type does poorly under nitrous oxid. Used ethylene with complete relaxation. (Lyons.)
Less bleeding—no cyanosis. (Lyons.)
More satisfactory than nitrous oxid. (Herb.)
Perfect relaxation. Excellent color. (Gaston.)

Opinion of the Patients.—Many volunteers for the preliminary work and some patients stated that ethylene was the best anesthetic they had ever had.

In our first publication we mentioned the possible advantages of ethylene over nitrous oxid. These advantages were surmises based solely on experiments with normal animals and healthy men. Each of these predictions was verified when put to the test in a clinic. For purposes of emphasis and as a partial summary, we repeat them here:

1. Anesthesia may be maintained:
   (*a*) In the absence of all signs of asphyxia.
   (*b*) In the absence of effects on blood pressure.
   (*c*) In the absence of dyspnea.
   (*d*) With complete muscular relaxation.

[3] They are, with the number of operations performed by each: Dr. Dean Lewis, 29; Dr. A. D. Bevan, 16; Dr. N. S. Heaney, 12; Dr. D. B. Phemister, 11; Dr. H. L. Kretschmer, 11; Dr. G. L. McWhorter, 3; Dr. E. D. Allen, 3; Dr. Gallagher, 3; Dr. Montgomery, 4; Dr. Gatewood, 1; Dr. C. B. Davis, 2; Dr. Edward Miller, 2; Dr. F. B. Moorehead, 2; Dr. Edwin McGinnis, 1; Dr. H. H. Everett, 1; Dr. Kellogg Speed, 1; Dr. Carey Culbertson, 1; Dr. G. E. Shambaugh, 1, and Dr. Vernon David, 2.

2. It may be used in obstetrics, a state of complete analgesia being possible at a concentration of 80% ethylene.

3. There is rapid recovery after long continued administration without evidence of after-effects.

Failures.—We frankly admit, however, 2 failures. In one the failure was complete, a concentration of from 90 to 95% producing in this young man marked cyanosis without the slightest relaxation. The other patient was rendered analgesic by a 95% ethylene-oxygen mixture, but was never profoundly anesthetized. At a subsequent operation under apparently identical conditions (except for the nature of the operation), surgical anesthesia was induced, together with complete muscular relaxation.

Such refractory cases are known to occur occasionally with nitrous oxid. In the past, no attempts have been made to determine why some patients are refractory to nitrous oxid or even to ether anesthesia. It seems to us that a group of such cases should receive a most careful study by all available means with the hope that such a study might possibly furnish evidence as to the mechanism of anesthesia.

COMMENT

On the basis of this clinical study, comprising a series of 106 patients with and without cardiovascular, renal and other complications, we can state briefly that ethylene-oxygen anesthesia is very satisfactory. Since it is possible to administer with the ethylene, on the average, as much as from 16 to 18% oxygen, asphyxia and its consequences are avoided, and cyanosis, so commonly seen with nitrous oxid, is conspicuously absent. Analgesia comes on surprisingly early. Considering, furthermore, that the relaxation is more complete than with nitrous oxid, we find that ethylene compares most favorably with ether. In fact, the impression is gaining ground that ethylene has some of the advantages of ether without many of its troublesome after-effects. The very prompt recovery points to a rapid elimination of the ethylene and may necessitate the administration of morphin immediately on the conclusion of an operation.

CONCLUSION

We append a note of warning to those who contemplate using ethylene in the clinic. Ethylene gas is inflammable. It forms, moreover, with air (or oxygen) an explosive mixture in a concentration of 4 volumes of ethylene with 96 volumes of air. Until further work,

now in progress, has been performed on its explosive properties, we warn surgeons and anesthetists not to use the gas in the presence of an electric spark, the actual cautery or a free flame.

Satisfied that, under proper conditions of administration (soon to be published by Drs. Herb and Lyons), ethylene gas produces in most individuals not only analgesia but also a state of surgical anesthesia incomparably better than with nitrous oxid for any kind of surgical work, we offer the gas to the medical profession for further trial in the clinic.

We feel that others who use it will be impressed with the rapidity and ease with which anesthesia is induced, with the slow and regular respiration, with the dryness and warmth of the skin, with the generally pink coloration of the skin and viscera, with the slowness and regularity of the pulse, with the absence of salivation, with the absence of blood pressure changes during or following considerable trauma and manipulation, with the complete muscular relaxation, and, finally, with the remarkably rapid recovery without serious sequelae after even a prolonged anesthetization.

In the meantime, we are continuing our investigations in the laboratory and clinic on various aspects which are of immediate importance.

GUSTAV FÜTTERER
1854-1922

Gustav Fütterer was born on March 7, 1854, in the small town of Peine, which lies a short distance from Brunswick in Hanover. He was the only son of a building contractor. He attended the Gymnasium at Hildesheim, but did not graduate. Contrary to his father's wishes, he went to sea, serving on the U. S. S. Tennessee. He then returned to Germany and completed his medical studies, first at Göttingen, then at Würzburg.

His dissertation, "A Case of Alveolar Sarcoma in the Anterior Mediastinum," gave evidence of an early leaning toward pathology. When we recall the association of Virchow with Würzburg, the great impetus which he had given pathology during the relatively few years that he spent here, such an interest is perhaps not unusual, the more so since Rindfleisch, professor of pathology during the time of Fütterer's studies, was himself an able pathologist and forceful personality. Fütterer became his assistant.

During the course of the next eight years he published a number of papers dealing with bacteriologic and pathologic problems, among them a careful study of the distribution of tubercle bacilli in the lesions of various organs in tuberculosis, one of the first pathologic reports of healed meningeal tuberculosis and a most important contribution to our knowledge of typhoid fever. In this he was the first to demonstrate the infection of the bile passages as well as the "carrier" state that ensues.

Carefully trained, imaginative and industrious although he was, his prospects for rapid advancement in German universities were unfavorable because he lacked the traditional classical premedical training. It required but little urging of American friends to turn his path again toward America as a future home, and he came to Chicago in 1890. He had married shortly before, his wife being the sister of Professor Jolly of Würzburg.

In Chicago he kept up his interest in pathologic problems. But he came at a time when experimental medicine was in its infancy, when work had to be carried out wholly on private initiative and with private resources. He had to devote much time to the establishment of a private practice that would be sufficiently lucrative to maintain his family in modest comfort.

GUSTAV FÜTTERER, M.D.
1854-1922

He was appointed a member of the staff of the Cook County Hospital and was for a number of years associated with the department of pathology at Northwestern. In 1902, he published a comprehensive monograph on the "Etiology of Carcinoma of the Stomach, Gall Bladder and Scrotum." He had devoted much time during the first ten years of his residence here to a study of carcinoma, and was one of the first to emphasize the rôle of ulcer in predisposing to carcinoma of the stomach and duodenum. His other publications during this period developed largely from his clinical observations and many of them are gastro-enterologic in character.

It is to be regretted that certain difficulties in establishing contact with medical circles that might have encouraged his experimental interests and utilized the splendid possibilities of his keen intellect and careful training led finally to the abandonment of a more strictly scientific career. He was no doubt better fitted for that than for active practice, successful though he was in it.

He was keenly disappointed in finding so little opportunity for the pursuit of his experimental activity. He was highly sensitive and felt that even his former German associates slighted his later work. As a result, he developed a degree of aloofness and made few personal friends, and these not among his medical colleagues. This undoubtedly has retarded in no small measure the appreciation of his work which its merit warrants.

He was professor of gastro-enterology at the Polyclinic for many years and was associated as consultant with a number of Chicago hospitals, among them the Columbus Memorial Hospital. He died there on Nov. 3, 1922, from heart disease.

WM. F. PETERSEN.

IMPRESSIONS OF DR. QUINE

In the following paragraphs I have undertaken only to describe some of Dr. Quine's characteristics as they impressed me, for I have elsewhere [1] given the detailed facts of his life so far as I know them.

When William E. Quine died, on December 7, it was a sort of ending to a chapter in the biographical history of Chicago medicine. Not that Dr. Quine was the oldest practitioner in the city nor the oldest one whose medical career was important, but he in a peculiar way represented the connecting link with a generation of medical notables who are gone. He began teaching fifty-two years ago; he was secretary of the Chicago Medical Society fifty-two years ago; he was president of the Chicago Medical Society forty-nine years ago. When it is remembered that only seven years ago, forty-two years after he was president of the Chicago Medical Society, he was the first president of the Institute of Medicine of Chicago, it will be realized how long he was in touch with important influences in medicine in the city and how long he was active in its medical affairs. And in another way Dr. Quine brought along the traditions of our elder worthies. He was ever susceptible to the influence of men that he admired, and in his impressionable period he came under the influence of N. S. Davis, Edmund Andrews and other strong personalities in Chicago medicine at that time, and their influence stayed with him as long as he lived. He tried to preserve their traditions; he believed in their ideals; the ambitions they inculcated remained his ambitions; and so he brought down to the present generation the best traditions of one of the strongest periods of medicine in Chicago. He was not a superficial imitator; he was a strong personality himself; his heroes in medicine were the vigorous men he had known; and he followed them not abjectly, but as an independent man who believed in his leaders.

He was peculiarly a product of Chicago medicine. He never studied or practiced medicine outside of Chicago. I have heard him regret the fact that he did not have at least enough European training in medicine to know some of the great teachers abroad. And I think he was right to some extent in this regret. I know nothing that destroys awe of great names like personal contact with their bearers; and I think Dr. Quine was a little bit less inclined to participate in national

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WILLIAM E. QUINE

1847-1922

activities in medicine because of a sort of timid overestimation of the men of national reputation, which would have been dissipated by more intimate contact with them. And I believe there were some influences of his early Chicago medical experience which were narrowing and which took him many years to overcome. Unless tradition is wrong, there was a good deal of acerbity and friction and suspicion of each other among the various groups which grew around the colleges and the big hospitals. The Rush group and the Chicago Medical College group showed a good deal of vigor in dealing with each other in matters of rivalry. The Chicago Medical College was in a way a protest against the Rush group, and the College of Physicians and Surgeons a little later a rival movement to both. Dr. Quine's early experience was in the midst of these none too friendly rivalries. When I first knew him I think I could still see traces of these influences. I can say also with exact truth that I thought I could see these old influences becoming less and less active with him, until in the last ten or fifteen years of his life I could see no trace of them.

Dr. Quine's career was molded in the unconscious view, which was practically axiomatic in his medical youth, that there were three forms of success in medicine—success as a practitioner, success as a teacher, and success as a writer. His leaders devoted their ambitions to becoming successful teachers and successful leaders in the practice of medicine, including, as N. S. Davis and Edmund Andrews undoubtedly did, endeavor to advance medicine in its public relations.

Material success in practice came to Dr. Quine early, and the other professional ambition of his life was devoted to becoming a great medical teacher. Medical teaching in that time meant the didactic lecture, and he made his forte the didactic lecture. He was purely a didactic lecturer. His clinics were really didactic lectures. There is no need to expound here how well he succeeded in this ambition. He would be named in any list of the half dozen best teachers in Chicago's medical history. It is the custom now to look down with complacent condescension upon the old didactic lecture system, and there is no need to worry about that. Men, however, are products of their own times, and it is doubtful that there are many among us at present who will give better accounts of themselves in present day teaching than Quine did in the teaching of his day. It is also a fashion among us to look with critical eyes at the didactic lecturers as talkers. That is

all Socrates was. We are probably overlooking a good deal when we forget the sum total of usefulness to students of such men as Davis and Andrews and Quine.

Dr. Quine lived nearly all of his life in Chicago, but he was by nature a Manxman. I do not mean that he cherished the Manx traditions more than the man of intelligence usually thinks about his origin, for he was heart and soul an American. But by nature he was a Celt: imaginative, sensitive, temperamental, impulsive, loyal, recognizing no bounds to the efforts he would make when his loyalty or his honor or his character or any of the abstract motives of life were involved. And this added to his interest as a personality. He was none of your cautious, reticent neuters. He was outspoken in matters that interested him and he was interested in the worthwhile things of life. His mind was active about them; he liked to talk about them, and he talked about them well. It made him an interesting companion and a valuable associate. He was independent. If he had views he was ready to support them. He was open to conviction, but he was impossible of coercion by either gross or subtle means.

Dr. Quine was not a ready maker of intimates; a sort of shyness held him away, I think, from intimacy with many men that he would have chosen gladly as close friends. He was rather abrupt in his manner and that also made him seem distant. But as a matter of fact he greatly enjoyed friends and was particularly fond of those whom he felt were within his intimate circle. In his later years he not infrequently spoke of the fact that he was lonely; as I have heard him put it, "I am just plain lonesome." He was fond of having his friends around him at dinners that he would give at his house. They were good dinners and delightful occasions. I went to such a dinner a few months before his death, when he had what he called some of his "old cronies" around him, and I remember on that occasion, as they were expressing their appreciation of his hospitality, he replied with evident deep sincerity that he was indebted more for the way they had come to him to relieve his loneliness.

He was an admirable man; he was generous and kind; he was honest and strong and he had an extraordinary mind. He is one of Chicago's medical worthies.

William Allen Pusey.

WALTER STANLEY HAINES
1850-1923

Dr. Stanley Haines died at the Presbyterian Hospital, Chicago, Jan. 27, 1923, of bronchiectasis and nephritis.

He was born in Chicago, Sept. 27, 1850, the son of John G. and Emma Adams Haines, whose family comprised, besides Walter, a brother, Charles, who died some years ago, and two sisters, Mrs. Beardsley and Mrs. Wirth, of Los Angeles, who survive.

The Haines family were among the early residents of Chicago and active in its social and civic life. His father was mayor of the city for two terms. He was also an ardent abolitionist, and his home, like that of some of his neighbors, served as a station of the "underground railway" for slaves seeking escape from bondage to Canada in the days before the Civil War.

Walter Haines attended the public schools of the city, graduating first in his class, from the Chicago (now the West Division) High School, in 1869. The list of graduates of this school includes the names of many men and women who have since risen to prominence, and they prize their membership in its alumni association quite as highly as the graduates of many colleges prize their degrees. The years 1869-1871 were spent at the Massachusetts Institute of Technology, and here were laid the foundations of his future career in chemistry. A serious attack of pleurisy—the first of many from which he suffered—interrupted his studies at Boston, and in 1871 he entered the Chicago Medical College (now the Northwestern University Medical School), from which he received the degree of M.D. in 1873. Thereafter he served an internship in the Mercy Hospital, Chicago. During 1895-1896 he spent several months in study abroad, mostly, at the Sorbonne, in Paris, and here he acquired that fondness for French science, art, literature and for the French people, which endured throughout his life.

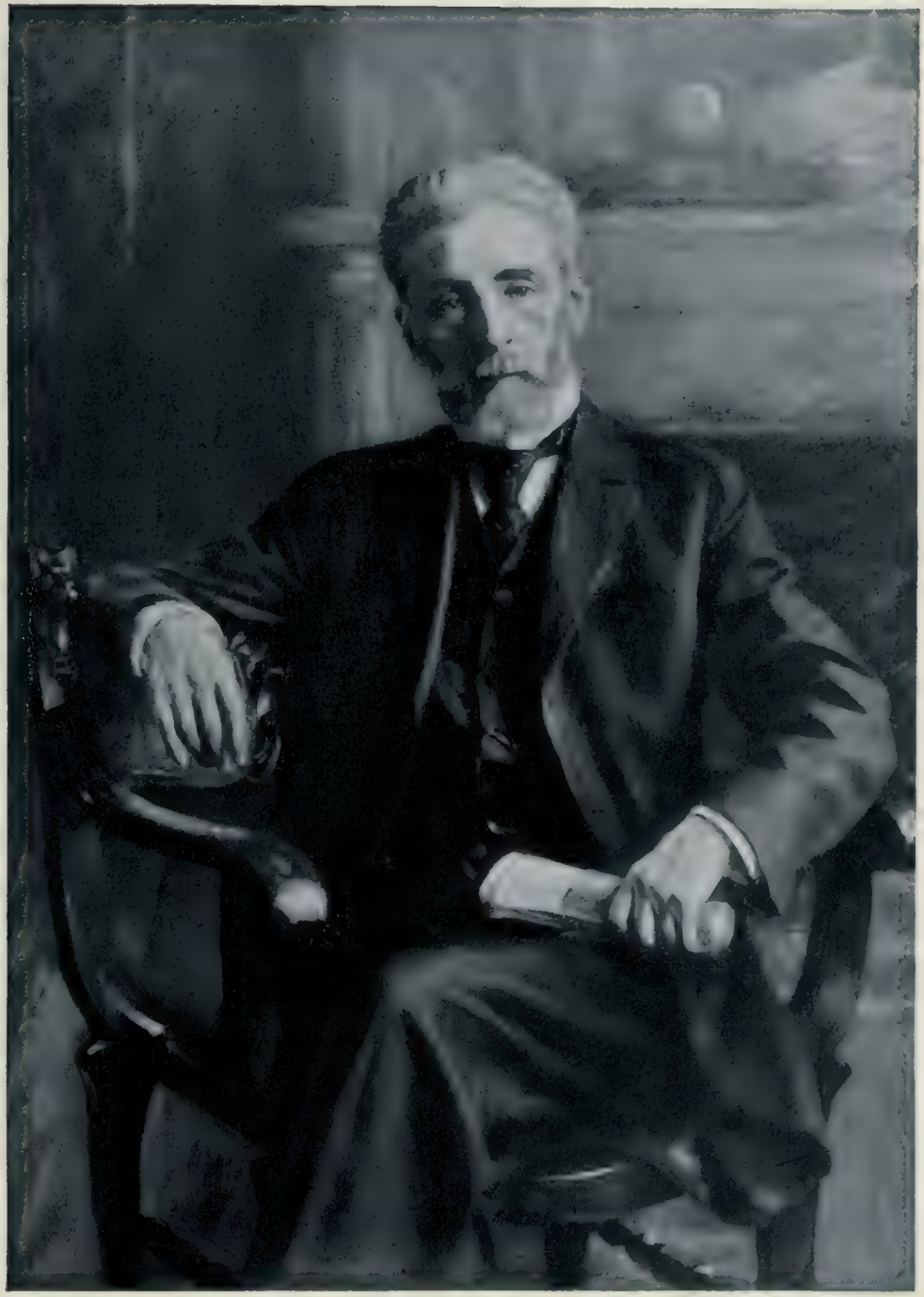
His thorough knowledge of chemistry and his aptitude as a teacher led to his being asked to give instruction in his medical Alma Mater while he was yet a student, in 1872, and to continue this work after his graduation. In 1876, the death of Prof. J. W. Freer, who held the chair of physiology and clinical medicine in Rush Medical College,

led to the appointment, as his successor, of Dr. Henry M. Lyman, then professor of chemistry. To the vacancy thus created in chemistry, Dr. Haines, then a young man of 26, was called, and he accepted. Here he continued to teach chemistry and later materia medica until almost the very day of his death—nearly half a century.

As an author, Dr. Haines was not prolific, his duties as teacher in classroom and laboratory taxing to the limit his time and his strength, which was enfeebled by repeated attacks of illness. He could recall fifty or more attacks of acute respiratory infection, many of them serious and protracted. I can recall, and can find record, of only two or three contributions to medical or other journals, one of them in collaboration with an assistant, discussing urinary findings in normal persons. And then there is the Haines' test for sugar in the urine, which became widely known and was of great usefulness. He was co-editor with Dr. Peterson of New York City, of a standard textbook on "Medical Jurisprudence and Toxicology."

He rendered service which was the equivalent of authorship, as a member of committees and commissions, in whose reports were incorporated many of his wise and helpful suggestions. He was a member of the Committee on Revision of the U. S. Pharmacopeia, 1900-1920, of the Illinois Food Commission continuously since 1909, of the Illinois Commission on Industrial Diseases, and of other similar bodies for shorter periods.

As a medicolegal expert, he was all his life in demand in both criminal and civil suits, and few men of his time were as capable and distinguished in this line. His unswerving adherence to the facts, revealed by his analyses and tests, the rigid care and thoroughness with which these analyses were conducted and controlled, combined with a remarkable faculty of explaining scientific facts and methods in language intelligible to those wholly unacqainted with chemistry or medicine, made his testimony most convincing to judge and jury and a formidable problem to the cross examiner. No abuse or heckling of the opposing side, however brutal and exasperating, could move him from his attitude of courteous, gentlemanly demeanor. The shrewder members of the bar early discovered the wisdom of refraining from the cross examination of Dr. Haines, for it almost always resulted in giving added force to his testimony. Some of the trials in which his cross examination was conducted by distinguished lawyers, who vied with



WALTER STANLEY HAINES, M.D.
1850-1923

him in quiet, courteous deportment, will long be remembered for their masterly, delightful word-fencing.

But it was to the teaching of chemistry, and later of materia medica to medical students that his life was mainly devoted, and to this service, together with that of friend and adviser of medical students, and as a member of the faculty of Rush Medical College in shaping the policy and conducting the college, he gave unstintingly of all that was in him for more than forty-seven years.

The teaching of chemistry to the medical students of thirty and more years ago was a totally, strangely different procedure from that of today. Many of the students of this early period, in Rush Medical College, as in other medical colleges, had little more than the ability to read, write and cipher. Of chemistry, many of them had only a vague conception and no knowledge whatsoever. To command the attention of such students, and to impart to them in a course of three or four hours a week, for a five months' session, repeated the following year, those principles, facts and methods of chemistry which seemed at that time to be most essential in medicine—was all that was possible. To drill these facts into the minds of such students in a way to make them stick and to be available for use at the bedside—to do this under the heavy handicap of repeated prostrating illness, which seemed many times to threaten the very life of its victim—that was a heavy task indeed, but no teacher of chemistry to medical students ever did it more successfully than Dr. Haines. He had in the classroom and laboratory, as he had on the witness stand, a remarkable faculty of clear, lucid, impressive statement. No student ever left his lectures with any valid excuse for failure to understand what had been said. The experiments presented to his class were always carefully set up after having been tried out beforehand, and they scarcely ever went wrong.

For the last twenty years he taught materia medica, and he was equally successful in engaging the interest of a much more highly educated and better prepared group of students.

Throughout his teaching career, his kindly manner, and his warm interest in his students led them to seek his advice, and they always met with a generous whole-souled response. He was especially fond of his laboratory assistants, one or more of whom he appointed each year from the student body. He had a fatherly interest and pride in their subsequent careers.

No teacher was ever more deeply and universally beloved by his pupils. Any member of the Rush faculty, meeting a graduate or a group of them, anywhere, at any time, was almost certain to be met by the query first of all, "How is Professor (or "Daddy") Haines? Be sure to remember us to him."

As a faculty member he was invaluable. Combined with a manner which was always modest, courteous and even deferential, was a firmness of conviction and a tenacious holding to his opinions. When however, after perhaps a vigorous debate, a faculty vote had decided on the course to be pursued, it mattered not whether the conclusion was in accordance with his views or otherwise—he was thenceforth a loyal, enthusiastic supporter of the course of action which had been decreed.

He was a member of the American Chemical Society, and the American Medical Association, the American Association for the Advancement of Science, the Illinois Medical Society, the Chicago Medical and the Chicago Pathological societies, the Institute of Medicine of Chicago, and other societies.

Dr. Haines was of slight physique—much like that of Dr. Oliver Wendell Holmes—about 5 feet, 5 inches in height, not much over 110 pounds in weight. An abundant crop of wavy hair, light tan in color, until it became gray, crowned a fine head, with clearly chiseled features. These were in part concealed by a mustache, and a short beard of the same hue as his hair. One of the most successful portraits ever painted of a medical man, or for that matter, of any man in this region, was the one of Professor Haines done by Nyholm, and presented by the alumni to the college in 1920. It hangs on the walls of the college.

He had a graceful, erect carriage, and a rather brisk gait in his earlier years. He was little given to gestures, for his clean, clear cut enunciation, his exquisite choice of words, and the systematic, logical arrangement of the material presented in his lectures, made them superfluous. A peculiar mannerism in conversation, of turning his head to the left and making a motion with his right hand as if to brush a speck of dust from his left shoulder, was characteristic. Sometimes his manifest effort to terminate a conversation without seeming abrupt or leaving the impression that he was in haste to get away for some other engagement, was touching, in that it prolonged the very "adieu" he was seeking. This effort was but a manifestation of his eager, uniform desire never to hurt the feelings of others.

He was one of the truest, most ideal *gentle*-men in every aspect of his personality—possessing a gentleness of manner, and of speech and conduct which was born of a supreme unselfishness which had always in mind the comfort and happiness of others as of prior importance to his own.

He never married, and the tender affection which he might have lavished on a wife was bestowed on his mother, his love for whom was a beautiful thing to see. She was a beautiful character—quiet, undemonstrative, but, up to the time of her death at 85, remarkably alert, a reader of the world's best literature, and thoroughly informed as to the affairs of her time. While she was living, Dr. Haines used to spend the week ends at her home in Waukegan (later with her daughter in Chicago), and these week-end visits were almost his sole relaxation from his daily routine of teaching. With her death, something seemed to go out of his life, and thereafter, his sisters removing to California, his life centered more and more wholly about Rush Medical College. His real home was his lecture room and laboratory—the boarding house or hotel where he slept, and the places where he ate, being merely incidental.

Although he lectured for many years, three or four times a week, and on many occasions demonstrated his ability to speak impromptu—always forcefully and with charm—he was modest and diffident to such a degree that he could never be persuaded to deliver a commencement or other address, or to represent the faculty at meetings of the alumni as he was frequently begged to do. When the alumni, gathered for a reunion at a state medical society or other meeting requested to have some member of the faculty to attend and address them, Professor Haines was invariably the first choice, but no amount of persuasion could induce him to accept such an invitation.

In such matters, as in the matter of resuming his work after an illness, or rather, while still sick, his resolution was adamant. He would do as he willed, in the face of all persuasion, injunctions, or orders to the contrary. So frail a body never contained a more inflexible will to do or not to do as he wished. Quite possibly this commanding will-power, which sometimes, especially to his attending physicians, seemed an unreasonable obstinacy, enabled him to drive himself to his work under a handicap of illness and weakness which would have compelled most men to succumb.

There has gone from us a chemical expert of unusual ability and attainment, one of the greatest of teachers of medical students, and a charming and lovable personality. Mingled with our grief is a feeling of gratitude that one so capable, so efficient, and so useful should have been spared for so many years to serve the medical profession and the public as teacher, adviser and friend.

We shall remember him not for the frail pain-wracked body which endured suffering so much and so long, but for the indomitable courage of a great soul that persisted at his work in spite of suffering, and for the fine spirit of the true gentleman, who had never an enemy, but numbered as a friend every one who came to know him.

John M. Dodson.

THE NEEDS OF OTOLOGY IN CHICAGO

REPORT BY SUBCOMMITTEE OF COMMITTEE ON MEDICAL NEEDS OF CHICAGO OF INSTITUTE OF MEDICINE

At present the practitioner is helpless to give relief in higher degrees of hardness of hearing, and attempts at prevention will be inefficient so long as the physiology and pathology of different parts of the ear are not better understood. The suppurations are fairly well known, but even here the diagnosis of the progress of a suppuration to the labyrinth, to the meninges or to the formation of a brain abscess is so uncertain that many lives are lost that should and might be saved, as the results of operation indicate. Similar conditions exist in the nose. The frequently unexplained fatal terminations after minor operations require close study. The great individual variations in the arrangement and size of the nasal cavities and the paranasal sinuses lead to many complications in the nose and its vicinity. In Chicago, the students of these subjects have to depend entirely on books and atlases (that is on 2 dimensions and reproductions), whereas 3 dimensions and the original specimen are all important.

It is evident that many lives may be saved by providing larger and better opportunities for the study of ear, nose and throat diseases. There should be opportunities for the careful, systematic examination of ear and nose patients in order to accumulate abundant material for complete microscopic study, in the hope that light may be thrown on questions of fundamental importance. A large collection of specimens of the ear and nose, at present not available, will be of great scientific, anthropologic and educational importance. It is clear that if any law or rule exists concerning the relation of the shape of the skull and the development of the mastoid cells and nasal sinuses, it can only become evident in a collection of this kind. It cannot be emphasized too much that the pathology of the ear is known in its outlines only; the filling in of important details is left for future investigation. Deaf-mutism is known only by general types. Of the pathology of the static labyrinth, the vestibule and semicircular canals, all that is known concerns the changes produced by suppuration of the labyrinth originating from the interior of the skull or from perforations from the middle ear and some of the congenital deformities. Progress can come only from the study of organs that have been examined closely during life.

It is true that in the medical colleges in Chicago efforts are made to teach students otology, so that they can pass the state examination, and efforts are also made in postgraduate schools to carry on this teaching, but for systematic investigation or individual work there are no adequate provisions either of space, equipment or material, and the inducements to make otology one's life work are small indeed.

A general program to meet the needs of otology—the establishment of a museum, the preparation of faultless series of labyrinths tested during life, investigation—can be carried out only in connection with a large clinic for the examination and treatment of patients. In order to obtain labyrinths, thousands of ears must be tested during life. Connections with deaf-mute societies and with hospitals of various kinds should be established for securing proper materials. Each test takes about one hour; in the beginning more perhaps, later less. The preparation of the labyrinth requires daily handling for from three to five weeks for each specimen. These considerations suggest what the scope of such an institution must be: At the head a director who gives practically his full time; a staff of 3 or more assistants to remain for at least 4 years, as it takes 2 years before one becomes trained for advanced work; and an indefinite number of voluntary assistants or externs. A sufficient nursing staff and laboratory attendants complete the personnel. The qualifications of the scientific staff of the institution demand remuneration and working conditions that will secure continuous and interested service. A board of advisory directors might well be composed of the head professors in the ear, nose and throat departments of the main medical schools in the city. A board of trustees, which may consist in part of laymen, completes the organization.

SUMMARY

The practical and scientific needs of otology in Chicago, that is, the best interests of the people, require the establishment of a separate institute of otology for the study and treatment of clinical cases and the accumulation of materials and specimens for the education of practitioners and the continuous scientific investigation of the physiology and pathology of the organs of hearing and allied structures.

GEO. E. SHAMBAUGH
J. GORDON WILSON
J. HOLINGER, Chairman

CINCHONA DERIVATIVES IN THE TREATMENT OF HEART DISORDERS *

K. F. Wenckebach
Professor of Medicine in the University of Vienna

Quinin has been used in treatment of heart disease for a long time, certainly for more than sixty years. I must confess that I have not had time in these last years to look up the history of quinin as a drug for the heart, but I have heard that Ludwig Traube, the most outstanding man in experimental work in connection with clinical findings, added quinin to digitalis to prevent or relieve the disagreeable action of this drug on the stomach. I do not know whether this is true or not, but it is so related. Among the older generation of clinicians there was a good number, and I knew some of them, who nearly always gave digitalis in combination with quinin. On being asked why they did it, they could not give me an exact reason; but they found that digitalis was better tolerated with quinin and that they could give larger doses without getting disagreeable symptoms. One of them said that not only he but also his patients were very much satisfied with this form of treatment, so why should he not give this combination?

My objection to the use of quinin in heart disease was that it had been shown by Santesson and by Stokvis to be a heart-paralyzing drug. Digitalis in toxic doses brings the heart to a standstill in systole; large doses of quinin, however, bring the heart to a standstill in diastole, and in smaller doses lead to a definite depression of the strength of the heart beat. This was the reason I did not wish to give quinin in cases of decompensation or any other bad condition of the heart. There I was wrong. We can never tell from the pharmacologic action of the drug how it will work at the bedside; for instance, we should never forget that the action of digitalis on the heart is mainly and primarily a depressing action on the functions of heart muscles, at least as far as its vagus action is concerned; and still digitalis is the most powerful and most brilliant of all heart drugs. That we should not avoid giving drugs that have been found to be useful at the bedside on account of theoretical arguments only is shown in the following case:

In 1912, a patient presented himself in my office wishing to get rid of attacks of auricular fibrillation. He knew that this was the so-called perpetual or complete arrhythmia and that his attacks usually

ceased spontaneously after from 2 to 14 days. He was a stout man, aged about 50, able to take a good deal of bodily exercise and even during the attack to walk for 4 or 5 hours. From this fact it was clear that the efficiency of his heart and circulation was only slightly diminished by the attack. He did not feel great discomfort during the attack but, as he said, being a Dutch merchant, used to good order in his affairs, he would like to have good order in his heart business also, and asked why there were heart specialists if they could not prevent this very disagreeable phenomenon. On my telling him that I could promise him nothing, he told me that he knew himself how to get rid of his attacks, and as I did not believe him he promised to come back the next morning with a regular pulse, and he did. It happens that quinin in many countries, especially in countries where there is a good deal of malaria, is a sort of drug for everything, just as one takes acetylsalicylic acid today if one does not feel well or is afraid of having taken cold. Occasionally, taking the drug during an attack of fibrillation, the patient found that the attack was stopped within from 20 to 25 minutes, and later he found that a gram of quinin taken regularly abolished his irregularity.

I was greatly struck by this fact, and afterward tried this sort of treatment in many cases of auricular fibrillation. My success was disappointing, in that quinin prevented auricular fibrillation in only a few cases and in those cases only when the onset of this form was quite recent, never when it was of several years' duration. At the same time, I found that even in those cases in which auricular fibrillation was not abolished, the drug had a marked soothing action on the often terrific rate of the ventricle. I received the impression that here the depressing, paralyzing action of the drug had a very favorable effect on the hyperactivity (hyperkinesis) of the heart. This made me try this form of treatment in other forms of arrhythmia also due to some form of hyperkinesis.

The first arrhythmia in which I had complete success with small doses of quinin (from 0.3 to 0.4 gm.) was extrasystole. It is well known that until that time we had no generally satisfying drug or method of treatment of this very common and innocuous, but at the same time very disagreeable, form of arrhythmia. For over 50 years I had been trying all of the drugs which one might expect to have a quieting influence on the heart. Besides digitalis in very small doses, which may work wonderfully in some exceptional cases, there was only

one drug which, I found unexpectedly, had a good influence on some of my patients, viz., strychnin. The first case which gave me proof of this favorable action of strychnin on extrasystole was that of a man with a serious insufficiency of the aortic valves. His heart was in a bad condition, and the man knew that he had only a short time to live. He bore his condition well, but there was one thing which made life unendurable to him, namely, periods of extrasystole. The extraordinarily strong pulse wave, following the compensatory pause of the extrasystole, made him feel so utterly miserable that he asked urgently for relief. I gave him strychnin, which has been given in other countries for many years in cases of heart failure. In doses of from 2 to 3 mg. daily, this drug helped him as soon as extrasystole came on, and the favorable effect was not lost until the end. I have found strychnin in these small doses helpful in cases of extrasystole in otherwise normal as well as in diseased hearts, but often it did not act strongly enough, or it lost its action very soon. In these last cases I tried the combination of quinin and strychnin and found that this form of treatment was completely successful in the great majority of my cases. I have given from 0.3 to 0.4 gm. of quinin daily, plus 2 or 3 mg. of strychnin through periods of 10 days. My experience with this treatment since the year of 1915 has been so favorable that I am convinced that those who try it will come to the same conclusion.

After seeing this favorable effect, I thought it wise to try quinin in other forms of hyperactivity of the heart. Quinin being a depressing drug, we have to be very careful in cases of damaged heart muscle or real heart failure; quinin cannot be a heart stimulant. Keeping this in mind, I have found that quinin treatment has its greatest use in conditions in which an abnormal rhythm starts in the auricle or the atrioventricular node, or when the ventricle interferes with the normal pacemaker of the heart. I have found it useful in all different forms of extrasystole and, to some extent, in the different forms of paroxysmal tachycardia; also in cases of marked so-called sinus arrhythmia starting in the normal pacemaker itself, quinin may act beneficially. Especially in those forms of tachycardia found so frequently in adolescence, in nervous, rapidly grown-up young people, quinin, especially in combination with strychnin with its marked vasomotor influence, may be of great help. This is of great importance, because these tachycardias, certainly of central nervous origin, are difficult to treat successfully. Administration of small doses of digitalis over a long period of time

sometimes has a favorable effect, but not in a really satisfactory way. The combination of quinin and strychnin stablizes the heart action so quickly, and the young patients are themselves so much relieved, that after a short time it is possible to start the most important and causative treatment, viz., mental and muscular training.

Favorable effects may be seen in other typical hyperactivity of the heart: In exophthalmic goiter and other forms of hyperthyroidism, not only does the heart beat too quickly, but the energy of every systole is much increased also, as if under the influence of constant stimulation of the accelerator nerves. Quinin in doses of from 0.4 to 0.5 gm. has a decidedly quieting influence on the heart quite apart from whether there is auricular fibrillation or not. The patient himself is the first to notice this favorable effect.

In view of all these beneficial effects, why is quinin active in so few cases of auricular fibrillation? Walter Frey's experiments are illuminating. Trying out the different derivatives of cinchona, he found that quinidin is much more powerful in preventing auricular fibrillation than quinin. The difference between the two seems to be merely quantitative. We found that by giving much larger doses of quinin we could get the same effect as by giving smaller doses of quinidin; but, on the other hand, in some cases of long-standing periods of extrasystole, quinidin had the full effect in cases in which quinin had been given for a long time without giving more than slight relief. Certainly, the introduction of quinidin as a form of quinin treatment has proved to be of the greatest advantage. The "dramatic" transition of long-standing complete arrhythmia into a perfectly normal mechanism of the heart has made a great impression on physicians all over the world and has made, this form of quinin treatment popular.

Summarizing my own experience and the work done by others, I may say that quinidin is most successful in those cases in which there is not much wrong with the heart, in which fibrillation has not been present for too long a time or in which it manifests itself in attacks as a special form of paroxysmal tachycardia. When auricular fibrillation is the only abnormal phenomenon of the heart, the disappearance of this disagreeable form of disturbance of the heart mechanism may be a complete cure, freeing the patient not only from his subjective symptoms but at the same time of the suspicion of having a myocarditis, or, at least, of some bad condition of the heart muscles. On the other hand, in cases in which fibrillation is only a part of the morbid condition,

when valvular diseases or pathologic changes in the heart muscles are the chief features of the disease, the preventing of fibrillation will give only partial relief. In such cases we should not forget that all cinchona derivatives are depressing drugs and should not be given in too large quantities. Generally speaking, in actual heart decompensation digitalis should be used, and it may be necessary to avoid quinidin until the condition of the heart is much better. I, myself, am giving the combination of digitalis and quinin from the very beginning, especially when there is a very rapid and irregular action of the heart, doing, as a matter of fact, what old clinicians did a great many years ago. To avoid an unfavorable effect of quinidin, one should try to find out whether auricular fibrillation plays an important rôle in the development of the disturbance of the circulation; with a slow ventricular rate there will not be much use for quinidin, and when there is a dangerous condition of heart muscle failure it may even do harm. Limiting quinidin treatment to cases in which fibrillation is a real factor of importance or the only symptom, one may see many cures and avoid the accidents mentioned in the literature. Certainly the last word in this important therapeutic matter has not been spoken, and careful observation of every patient under treatment will be necessary before we shall know all we wish to know about quinidin treatment in auricular fibrillation.

The great impression that quinidin treatment has made on the medical profession is certainly due to the fact that its favorable effect shows itself suddenly by the transition of long-standing irregularity into normal rhythm after the administration of the drug. It is this sudden effect that gives absolute proof of its activity. Would it not be possible to get the same form of convincing proof for the action of quinin in those other forms of irregularity of which I have been speaking? This proof has been provided by Winterberg. He found in my clinic that intravenous injection of quinin (not quinidin) stopped an attack of paroxysmal tachycardia in many cases, sometimes so quickly that he had to keep his electrocardiograph running in order not to miss the interesting moment of transition from the pathologic to the normal rhythm. In a few specimens of tracings the sudden stopping of the attack was obtained by the injection of not more than 0.5 or 0.75 gm. of quinin, a dose perfectly tolerated by all our patients and much smaller than the doses injected intravenously in cases of long-standing or severe tropical malaria. The patient has the curious sensation of a heat wave passing through his body, but no other disagreeable effect; only rarely

did we have to deal with depressing actions of quinin on the tonus of the vessel wall, showing itself in a fall of blood pressure and sometimes in syncope, easily relieved by stimulants. The same favorable effects of the intravenous injection are shown in one of these tracings from a case of extrasystoles coming on in long series that resisted quinin treatment by mouth, so that proof of the favorable action of quinin on extrasystole, so evident but not showing itself so immediately in treatment by mouth, is given in a way absolutely equal to that of any form of experiment.

It would take too much time if I should try to deal broadly and deeply with the question of the analysis of the action of quinin on the heart muscle. This question requires a great deal more experimental work: certainly, it is not sufficient to say simply that quinin lengthens the refractory period of the heart. We must investigate the effect of quinidin on every single function of the heart muscle and distinguish between its primary and its secondary effect in the way Engelmann taught us. What this means may be exemplified by the well-known fact that digitalis, which lengthens the conduction time, may have a favorable effect even in cases in which there is a lack of conductivity. This favorable effect is due to the fact that digitalis at the same time both slows the heart and provides it with a longer time for restoring its various functions.

Before leaving this subject I want to say a few words about another influence of quinin bodies which may prove useful in the treatment of cardiovascular conditions: the syncope just mentioned is generally and probably rightly ascribed to vasodilatation, not so much to depressing action on the heart. Some clinical observations have shown that in so-called vascular crises (sudden spasm, i. e., hyperkinesis of the walls of the smaller arteries) quinin may stop the spasm and so relieve the patient of his symptoms. Winterberg found that in some cases of anginal pain accompanied by a sudden and important rise of blood pressure intravenous injections of 0.5 gm. of quinin may stop the attack at once and completely, so that not only the pain but also the enormous rise in blood pressure is abolished. Winterberg has described the details of this interesting case. I simply want to point out that the problem of quinin in the treatment of heart disease and cardiovascular conditions covers a much larger area than the question of quinidin and auricular fibrillation, and that the action of this drug on the arterial system and its rôle played on the circulation in general should be studied carefully.

That quinin must be of the greatest importance in the treatment of such conditions was known to the old clinicians. The Viennese clinician Oppolzer, in his lectures on the treatment of internal diseases (1872), began his chapter on the treatment of heart diseases with the words: "The best and most powerful factors in dealing with heart patients are three: rest, digitalis and quinin." Curiously enough, all of us had forgotten about quinin. Certainly, we did not know exactly in which cases it should be given, and we had insufficient experimental evidence about its action, knowing only that it is a heart-paralyzing drug. I, myself, avoided quinin only on this theoretical reasoning. The facts now known teach us that the last word in therapeutics has to be said at the bedside—but, at the same time, that experimental evidence and careful analysis of the action of the drug will give us a clearer insight into the important question as to the cases in which it should be avoided. I think all will see that the reintroduction of quinin into therapeutics not only is an important acquisition in the treatment of heart disease, but that at the same time it gives us a practical and splendid instance of the cooperation of clinical and experimental investigation.

THE GENERAL PRINCIPLES OF ORGANOTHERAPY

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By organotherapy we understand the partial or complete control of the disease due to hypofunction of an organ by oral or parenteral administration of substances prepared from this organ. This field of therapy can now be credited with two distinct successes, but it is also handicapped by not a few unproved claims, and many baffling failures. For any one to attempt a guiding orientation in the present confusion may seem both presumptious and foolhardy. Still, a few footnotes to selfevident principles may help to clarify. In presenting these principles and comments, I claim neither originality nor infallibility.

1. *Successful treatment of the symptoms of hypofunction of an organ by extracts of said organ requires that the essential function of the organ consists in producing a substance or substances in the nature of hormones.*

It follows as a necessary corollary to this principle that organotherapy is out of the question in the case of tissues in which the production and storage of such substances are either absent or of no fundamental importance in the function of the organ. The lung tissue permits or produces the exchanges of oxygen and carbon dioxide between the blood and the air. So far as we know, the lung tissue stores no substance that can in any way facilitate lung function or act as a substitute for the living lung; hence, the certain futility of lung extract therapy of pneumonia or pulmonary tuberculosis.

The same general situation exists in regard to the kidneys and liver, the nervous tissue in general, the heart and other muscular tissues, and possibly other organs. No amount of flooding of the body fluid with kidney extracts can separate the urinary constituents from the blood in the absence of living kidney cells. The liver plays a complex rôle in the body, and part of its function may be the production of important hormones; but other important liver functions, such as glycogen storage, protein deamidization, synthesis of urea from ammonia, desaturation of fats, bile formation, etc., cannot be carried out by liver extracts. The futility of organotherapy in the cure of defects or destructive lesions of the nervous tissue is equally apparent.

The only possibility for organotherapy in the case of the tissues just referred to is the chance or evidence that these tissues produce substances capable of stimulating the impaired organ or organs to increased activity.

For example, the kidney may contain a substance that stimulates the living kidney cells to increased secretory activity although the substance itself cannot secrete urine. It is supposed, for example, that the mammary glands contain lactagogue substances. Substances may be prepared from the gastric mucosa that induce secretion of gastric juice when injected into the blood. The liver contains a cholagogue in that it contains bile elements. Nervous tissue is rich in lecithin, and some have held that administration of lecithin is favorable for the growth and metabolism of nervous tissue, etc.

The existence of such specific organotropic substances in these various organs must first be demonstrated by accurate laboratory experiments before one is justified in using such organ extracts on patients, where even under the best of conditions all the factors cannot be controlled. The indiscriminate use of tissue extracts in maladies of unknown or complex origin leads to confusion. One can place little credence in the results of such clinical use of organ extracts until supported by laboratory experiments on animals. This principle must be insisted on all the more since many of the clinical lesions of the kidneys, lungs, liver and brain can be reproduced experimentally in animals.

A typical case in point is the testicular "spermin" of Poehl, which was proclaimed as a general metabolic stimulant, and for a time used as a "cure-all" by a few uncritical enthusiasts.

2. *There is little or no hope for successful organotherapy in diseases due or supposed to be due to a primary hyperfunction of organs.*

When a malady is definitely traced to primary hyperfunction of an organ the remedy is surgical (direct or indirect), not medical. But the question of an out-and-out organ hyperfunction including serious clinical disorders is at present a complex and uncertain chapter in medicine. Gastric hypersecretion or hyperacidity is supposed to cause certain symptoms in gastric and duodenal ulcers, and in so-called vagotonia. The syndromes of toxic goiter, acromegaly, hemolytic jaundice, and certain types of anemia, hypergenitalism, and osteomalacia are held by some biologists and clinicians to be caused by hyperactivity of the

thyroid, hypophysis, spleen, pineal body, suprarenal cortex and gonads, respectively. If it is clearly established that sufficient hyperactivity of these and other ductless glands cause disease, the only type of organotherapy that may be of value is the administration of organ extracts that depress the hyperactive gland—if there are such extracts. For example, it has been reported that administration of ovarian extract to young males retards the development of the testes, and the observations of Lillie on the freemartin seem to show that the testicular and ovarian secretions have some mutual inhibitory action on the development of the respective sex characters. But the work of Moore reveals no such antagonism between ovarian and testicular hormones after birth of the animal. This type of organotherapy is empirical and should be well grounded by animal experiments before it is applied to patients. If the hyperactivity of a gland is a compensatory one, administration of extract of that gland might arrest the growth of the gland but would not control any other symptoms. The "hyperplasia" that may be induced in some endocrine glands by extirpation of other endocrine glands is no evidence that the extirpated glands secrete hormones holding the other glands in check. Hence there is at present no basis for a pituitary organotherapy for toxic goiter. If the glandular hyperplasia and hyperactivity is primary, such organotherapy is clearly contraindicated.

3. *There are at present no definite indications for organotherapy in disease due or rather supposed to be due to organ distrophy, that is, a perverted or pathogenic secretion.*

The theory of a perverted or pathogenic secretion as the cause of disease has been advanced for some of the maladies related to the ductless glands, notably the thyroid and hypophysis. The theory has little or no basis in fact. But assuming that it is true, the following possibilities must be considered: (1) The gland may yield both the normal and pathogenic secretion. In that case the patient will show no symptoms of glandular hypo-activity, the symptoms of the disease being solely due to the perverted secretion. In such a case specific organotherapy would in all probability prove useless, and there is no reason for believing that the normal secretion of the gland would control the pathologic secretion. (2) In yielding the pathologic secretion the gland may be so altered that the normal secretion is diminished or absent. This is the most likely condition. In such a case the syndrome would

be a complex of glandular hypo-activity and pathogenic secretion, and it is obvious that organotherapy might have a favorable effect on the hypoglandular symptoms but leave the pathogenic secretion symptoms unaffected.

4. *The hormone or hormones must be stored up in active form and in some quantity in the organ producing them for successful organotherapy of this organ.*

It is obvious that unless the specific hormone in question is stored in the gland to some extent, administration of the gland extract in hypofunction of the gland will be useless. For example, a glycerol extract of gastric mucosa contains pepsin, but no hydrochloric acid, although both of these substances are produced by the gland cells and are of equal importance in gastric function. The reason is evident. Pepsin is stored up as pepsinogen in the resting cells, while the hydrochloric acid is not stored up but discharged from the cell as soon as formed. Hence a gastric mucosa extract contains the former but not the latter, and in organotherapy of the gastric mucosa hydrochloric acid must be added from some other source. Analogous conditions may obtain in some of the endocrine glands.

In addition to knowing how much of the secretion is stored in the gland, it is important to know how immediate or urgent is the body's need for the secretion, and how long the latter remains in the body. Light on these questions has been obtained by determining how soon symptoms appear after removal of the glands. Taking two extremes, it has been found that symptoms may not appear for weeks or months after removal of the thyroid, whereas they appear within from 4 to 8 hours after removal of the pancreas, and they may appear within a few hours after removal of the parathyroids or the suprarenal cortex. It is evident that the chances for successful organotherapy are much more favorable in the case of the thyroid gland.

5. *The physiologically important hormone stored in the gland must be sufficiently stable to resist the necessary chemical processes of making the gland extract; and, for practical organotherapy, the hormone must resist the action of the digestive enzymes and must be absorbed into the blood in active form.*

This is probably the most serious limitation of organotherapy. All hormones are probably (in fact, *must* be) soluble in serum or

Ringer's solution. But because of the necessity of continuous or daily administration, intravenous or hypodermic injections of extracts of the entire glands produce toxic effects, in some cases more serious than the symptoms treated, owing to the presence of injurious tissue split products. The chemical manipulation necessary to remove these toxic by-products introduces greater chances for destruction or loss of the hormones themselves. Moreover, intravenous or hypodermic injections must as a rule be made by a physician or a nurse, and even when this is done there are chances for local or general infections when employed daily or several times a day for months and years. This is one of the difficulties of the present "insulin" therapy of diabetes. *Practical organotherapy, then, limits itself in most cases to administration of the gland or gland extract by mouth.* That is, the hormone must run the gamut of the enzymes both in the lumen of the alimentary tract and in the wall of the absorbing intestine. In view of this fact, the failures of organotherapy are less surprising to biologists than the one striking success in the case of the thyroid. If the founders of thyroid organotherapy had known of the general completeness of the protein and fat hydrolysis in the digestive tract, we believe they would scarcely have had courage to try the feeding of thyroid in myxedema and cretinism.

Classical examples of destructive action of the digestive enzymes on hormones and alleged hormones, or failure of these hormones to reach the tissues in active form when administered by mouth, are epinephrin, pituitrin, "insulin," and the pancreatic and gastric "secretins."

6. *The hormone must be present in the gland in active form; be activated by the chemical processes of preparing the extract or the normal activator added to the gland or the extract.*

The thyroid hormone, epinephrin, pituitrin, insulin, are present in the glands in active forms or are activated by the processes of extraction. Whether any of the other internal secretions are stored as prehormones and must be activated in or by the products of other organs has not yet been determined. Münser assumes that all the endocrine glands work in pairs, one activating or inhibiting the other. He therefore concludes that before an organ is used in organotherapy it must be "activated" by previously removing the inhibiting gland from the animal. For example, before using the pancreas of an animal to control

pancreatic diabetes in a patient, the animal must have had the anterior lobe of the hypophysis extirpated some time before the pancreas is excised in order to yield an "activated" pancreas. This fanciful theory is not borne out by the well established facts of thyroid organotherapy, and I shall point out later that extirpation of some of the alleged inhibitors of the suprarenals do not influence the epinephrin content of the gland.

Hedon claims that when the blood from the pancreatic vein is introduced into the portal circulation of a diabetic animal, there is a diminution of the glycosuria, while it has no effect when introduced into the general circulation. Thus, he concludes that it is necessary for the internal secretion of the pancreas to reach the liver in order that it may be active. But it is a fact that the establishment of an Eck fistula in animals does not induce hyperglycemia and glycosuria on ordinary carbohydrate rations, despite the fact that by this operation all the portal blood, including that from the pancreas, is sent into the general circulation before a small fraction of it reaches the liver by way of the hepatic artery. Hedon's theory is untenable in view of this fact. But we have a classical example of such "distant activation" in trypsinogen and enterokinase; and the possibility of analogous conditions in the ductless gland, where all attempts to isolate or demonstrate active hormones have so far been failures, must always be kept in mind and tested.

7. The hormones must be relatively stable in the form in which the gland or gland extract is put on the market for therapeutic purposes; and the organ preparations must, so far as possible, be chemically and physiologically standardized.

No argument is needed in defense of this principle, although it is not always complied with. Stability of the hormones may not be attainable, in which case we must have recourse to fresh glands or fresh extracts. The only criticism that may be legitimately directed against manufacturing concerns in such cases is for failure to indicate the date of preparation of and the rate of deterioration of the extract. While pancreatic secretin has so far proved to be of no therapeutic value, it can be prepared in active form, but not kept from rapid deterioration, so that the preparations on the market become inert in a few weeks. This would be serious in case the active secretin was of any value in curing and controlling disease.

The chemical and physiologic standardization of such substances as thyroid, pituitary, and suprarenal extracts is just as important as the standardization of diphtheria antitoxin. It should be insisted on by the profession, and required by law, in view of the fact that the preparations on the market show such great variations in physiologic activity. This is obviously a great drawback to the successful use of these substances in disease. The standardization of "insulin" is imperative in view of the serious consequences of an overdose of this substance.

The importance of chemical and physiologic standardization of preparations of the parathyroid and the corpus luteum is equally obvious. The parathyroids are very small organs, distributed on and in the thyroids, and, in some cases, in the thymus. It takes a good deal of training and care to avoid the inclusion of small accessory thyroids or nodules of thymus in gathering fresh parathyroid material. There is some evidence of variation in the function of corpus luteum with the age of this temporary organ, and with the incidence of pregnancy. Even the most careful manufacturer, therefore, is facing great difficulties, since his only sources of material are the abattoir animals, and his only evidence of the state of ovulation in the abattoir animals is the appearance of the ovary by direct inspection. Dannereuther states that only one of the several drug firms that place ovarian products on the market would affirm that their corpus luteum preparations are made from the corpus luteum of pregnant animals. There exists, at present, another serious source of error or cause of discrepancies in therapeutic effects in the usual practice of removing fats or lipoids from the dried products or solutions of such organs as the ovary, the hypophysis and the suprarenal cortex. The solvents that remove the lipoids may also remove the hormones. Until the hormones have been actually isolated it would seem more promising to use the entire gland, at least when given by mouth.

8. *In case of the endocrine glands in which organotherapy is still in the balance, the clinical use of organ extracts should be most rigidly controlled and should be preceded or paralleled by animal experiments.*

Empirical organotherapy is not to be condemned entirely, but when organ extracts are used in this way without the guidance or positive indications from physiology or experimental pathology, medical progress demands that other factors be eliminated so far as possible, so that

the results may have some meaning. A careful perusal of the literature will convince any candid man that we are great sinners in this regard. The other factors referred to are: (1) other therapeutic measures such as changes in diet, occupation, environment, etc., simultaneously instituted; (2) the elements of suggestion; and (3) the natural history of the malady. For example, if we disregarded the natural course of colds, or mumps, or chorea, we could readily establish a splendid organotherapy of these diseases. This is too obvious to mention, except for the fact that our literature demonstrates that it is so frequently forgotten. Our age has been characterized medically as one of therapeutic nihilism. On the contrary, *in the field of ductless glandular diseases and organotherapy, it is an age of therapeutic credulity and foolish faith in the biologic and medical omniscience of drug manufacturers.*

The ideal scientific control is not easily attained in most clinical cases. There are the spontaneous fluctuations in the severity of symptoms, spontaneous repair irrespective of all therapy, and factors of general hygiene and nutrition which the good physician always endeavors to improve. There are the uncertainties of diagnosis, especially in the so-called pluriglandular diseases. Hence the value of the guide and aid of definitely controlled animal experiments. Clinical results will ever constitute the final test of organotherapy in any given condition, but intelligent cooperation of the clinic and the laboratory will assure a quicker arrival at the truth.

9. *The dangers in organotherapy.* When, as in the case of the thyroid, oral administration is effective, this method should be used exclusively, as a routine procedure. There is danger in giving overdoses of thyroid extract, even when given by mouth, but it seems that all of the other endocrine preparations can be administered per os in large doses, and for long periods, with little or no deleterious effects. There may also be no evidence of beneficial effects, but that is another story. We are now concerned with the *dangers* of organotherapy.

Intravenous organotherapy is the most dangerous; hypodermic and intramuscular administration is less dangerous than the intravenous route, but hypodermic injections of crude organ extracts are capable of seriously injuring the patients through (1) anaphylaxis, (2) toxic protein derivatives (histamine, peptones, etc.); (3) toxic lipoids (cholin, neurine, etc.), (4) local damage of tissues at the site of injection. Hence as a general principle, *organ extracts of unknown composition*

(and this includes all of them except thyroxin, epinephrin and with some reservations, pituitary extract and insulin) must not be given intravenously or hypodermically when repeated administrations are called for. Crude endocrine products parenterally administered introduce the additional complication of nonspecific protein therapy. We must clearly recognize that intravenous or hypodermic therapy is always unphysiologic, and should be used only with pure products, and when the oral route yields no results, or too slow effects.

The principle laid down in this paragraph puts a serious task before the manufacturer of organotherapeutic products, a task demanding the highest grade of scientific ability, and complete integrity; in fact, a higher type of accuracy and integrity than that required in ordinary so-called honest business.

10. *Early versus late therapy in endocrine hypofunctions.* The importance of early diagnosis and therapy of hypofunctions of the ductless glands is obvious, since the early therapy may check further deterioration in the gland system primarily involved, and prevent the development of nonreversible atrophies or abnormalities in other organs. Early therapy may thus be effective, while late treatment is less effective or even noneffective.

While we all subscribe to this principle, the great difficulty comes in the application, from the fact that *none of the incipient symptoms of hypofunction of any endocrine system are specific.* For example, the primary etiology of slight nervous disturbances, slight adiposity, slight disturbance in growth, slight disturbances in sex functions, slight disturbances in metabolism, slight mental retardation or inferiority, etc., may be entirely outside the endocrine field. Early diagnosis becomes therefore essentially guessing, and the meaning of positive results of organotherapy based on a guessed diagnosis, becomes also a matter of guess. This is undoubtedly one of the most disturbing factors in evaluating the results of organotherapy. How are we to proceed with fairness to the patient in the face of the following facts:

(1) None of the incipient symptoms of endocrine hypofunction are specific.

(2) Slight hypofunction of any of the endocrine glands may be only temporary, with spontaneous recovery. Any therapy of such conditions is apt to lead us to wrong conclusions, and thus impede the progress of medical art and science.

(3) Prolonged and marked hypofunction of at least some of the ductless glands (e.g., the thyroids, parathyroids) induces a more or less irreversible pathologic condition in other organs, rendering late therapy less effective.

What is the physician to do in this dilemma? Is he to apply an indiscriminate or pluriglandular therapy in incipient and uncertain cases on the chance of a random hit, or is he to await developments, thereby possibly harming the patient?

It would be presumptuous for any man to dictate the line of conduct here, but I think the following points are within reason:

(a) When the diagnosis is a guess, let us all admit the meaning of therapeutic results is also a guess.

(b) Internists as well as laboratory men should make greater efforts to work out reliable criteria of incipient endocrine hypofunctions, and determine more clearly the time factor of the irreversibility of endocrinopathic sequelae.

11. *Uniglandular versus pluriglandular organotherapy.* In recent years there has been a tendency to abandon the use of single gland products in favor of gland mixtures. This tendency has been particularly marked in the case of the thyroid, the hypohysis, the gonads, and the suprarenal cortex. We do not include here the extreme tendency in this direction—the inclusion in organotherapeutic mixtures of extracts of organs (like the kidney, the lymph gland, the spleen, the brain, etc.) when evidence of endocrine function is entirely lacking, and the use of these mixtures as general or "supportive" therapy for all kinds of disorders. This is quack practice rather than medical practice. The combined administration of extracts of organs of known or probable endocrine functions as empirical therapy is based on the following considerations:

(1) There is some evidence of mutual interdependence of some of the endocrine glands. Thus the normal functioning of the gonads depends, among other things, on the thyroids, and possibly the hypophysis, and the suprarenal cortex. Extirpation of the gonads leads in some species to changes in the hypophysis, thymus, and the suprarenals.

(2) Endocrine glands like the thyroids or the pancreas that have fundamental influences on the general metabolism and growth will necessarily influence the other ductless glands as well. But apart from this the theories of specific influence (stimulation or inhibition) of one ductless gland on others rest on precarious foundations. But it is quite

probable that conditions such as all dietary deficiencies and chronic and acute infections have some effects on the entire endocrine system, more so on some than on others.

(3) The foregoing consideration has led to the theory that endocrine disorders are seldom or ever confined to single systems, that they are, in fact, pluriglandular. The corollary to this theory is the pluriglandular therapy of these diseases. But it must not be forgotten that in the experimental animal specific diseases are produced by damaging specific ductless glands, and so far as organotherapy is at all effective, it suffices to administer the product of the damaged gland to control the disease. It is not necessary, for example, to add pituitary, gonad, or suprarenal cortex to the thyroid extract to control experimental cretinism or myxedema.

(4) Fortunately, to date most pluriglandular therapies have been administration of the mixtures by mouth. In this way the least damage is done to the patient. But the spacious theory that we can supply the human body with any quantity or quality of endocrines, the internal coordination being so perfect that the body cells pick out only the kind and quantity of hormones needed, is not only without basis in demonstrated facts, but is in some instances (as the thyroid, and possibly the hypophysis and pancreas) definitely contradicted. The fact that most of the endocrine products are more or less inert when taken by mouth, probably explains much of the success of the pluriglandular therapy in the hands of the uncritical.

(5) But, it may be argued, all these considerations and objections to pluriglandular therapy are academic and beside the point. The whole matter is: Does the patient improve or get well on the pluriglandular diet? That is the crucial question. We can throw the rationale to the wind, provided the patient improves and does not have a relapse when he receives our bill. All systems of healing point to successful cures, to the crucible of their clinics. But will you not agree that we must examine the crucible? Pluriglandular therapy as frank empiricism is not to be wholly condemned, even in the 20th century. But it increases the chances for post hoc falacies, as few men are content to be mere pupils to the detail man. We do try to think or imagine we do think.

It is, perhaps, significant that thyroid extract (the one substance active per os) is so frequently an ingredient in the ready to serve pluriglandular mixtures, just as alcohol and laxatives make up part of

many otherwise inert patent medicines. For example, one manfacturing concern lists 10 different pluriglandular mixtures, and 7 of these are said to contain thyroid extract:

"Orthophrenic" (thyroid, pineal, testes-ovary, prostate, cerebrospinal substance, activating substance).
"Virilogenic" (anterior lobe, suprarenal cortex, thyroid, testes, prostate, activating substances).
"Galactagogue" (mamma, placenta, posterior lobe, thyroid, activating substances).
"Morphogenic" (thyroid, suprarenal, pituitary, pineal, thymus, activating substances).
"Catabolic" (thyroid, posterior lobe, suprarenal medulla, sperminum, activating substances).
"Feminilogenic" (pituitary, suprarenal, thyroid, corpus luteum, ovary, mamma [virgin], activating substances).
"Osteoplastic" (thyroid, pituitary, parathyroid, suprarenal medulla, thymus, activating substances).

We are not informed what the "activating substances" are, except in the case of the thyroid, where it is said to be iodides. The use of these mixtures thus amount practically to dosage of the patient with thyroid extract and potassium iodide.

12. *Experimental versus clinical organotherapy.* Despite the minor difference in species in the kind and severity of symptoms induced by specific endocrine pathology, and minor species differences in the effects of organotherapy, it is a striking thing that in all securely established facts of endocrine diseases and organotherapy, there is a practically complete parallel between the experimental animal and man. We need mention only the thyroids, the parathyroids, the gonads, the pancreas. This fortunate fact rendered possible the rapid advance in the analysis of the endocrine diseases during the last fifty years. This fact also tends to render the laboratory investigator skeptical in relation to therapeutic results on man that cannot be duplicated in the laboratory, especially if the clinical reports include such variables as guessing the diagnosis, several synchronous therapies, and inadequate controls in the way of the natural history of the disease. The clinician, on the other hand, perhaps knowing less intimately the evidence for the unity of life and organ function in mammals, is apt to become impatient with the strictures of the laboratory worker, and undervalue the significance of experimental data in the analysis and cure of human ills. "After all," they say, "the final arbiter is the crucible of the clinic." But so far as the clinic is or can be a crucible, it is identical with the crucible of

laboratory research. The following seems obvious: (1) certain nervous manifestations of endocrine pathology, especially in the group of consciousness, may differ in man and the dog, and the laboratory man must admit that conscious nervous manifestations cannot at present be studied with accuracy in the experimental animal. For example, there is nothing definitely known in the spayed bitch identical with the neurocirculatory disturbances of the spayed woman. And when the internist reports that these neuroses of the premature menopause in his patients are ameliorated by ovarian therapy, the laboratory man has nothing to say, except the obvious remark that nervous symptoms relating to sex, especially in women, are often profoundly influenced by suggestion. The menstruation phenomena in women are not completely duplicated in the rut of the lower animals. But as regards the other really objective findings of gonadectomy and gonad therapy after castration, there is no quarrel between the clinician and the physiologist.

Both groups must also admit the *possibility* of differences in actual physiologic effects of organotherapy *per os* in man and the laboratory animals. As pointed out above, hormone given by mouth must pass the following obstacles before reaching their field of action (the blood and tissues); the destructive action of the digestive juices, the destructive action of the intestinal bacteria, and exclusion or destruction by the intestinal mucosa. So far as we know, the digestive ferments are identical in all mammals, but there may be species differences in intestinal flora and intestinal permeability. Such differences, however, must be demonstrated, not merely assumed.

13. *A complete organotherapy is probably not attainable.* In the normal animal hormone equilibrium is balanced by delicate chemical and possibly by equally delicate nervous processes. When this equilibrium is upset by disease, it is probably impossible to restore complete balance by our relatively crude methods of organ extract administration. In complete absence of the thyroid gland, thyroid therapy greatly improves the man and the experimental animal, but they do not come up to the normal level. At present insulin therapy does not entirely replace the pancreas. And even so, we may place thyroid extract and insulin in a class by themselves, for organotherapy of all the rest of the endocrine glands is still in the balance.

This statement of the obvious would not seem complete without "case reports." I have selected two, one, purely clinical, the other partly experimental.

Case 1.—Not long ago there appeared in a reputable American medical journal a report on 1,000 hypodermic injections of fresh testicles of goats, boars, rams, and deer, into 656 persons, including 7 women and 13 physicians. What ailed the 7 women that our colleague could hope to cure by goat testes administered hypodermically is not related, nor are we told what ailed the 13 physicians, but all except one reported "good results," and as a class we are paid this astonishing compliment: "it is extremely doubtful that suggestion played a rôle." I wonder whether the gold-brick venders' guild is in equally extreme doubt as to our insusceptibility to suggestion. I pass over the therapeutic benefits reported from this therapy in general asthenia, rheumatism, acne vulgaris, neurasthenia, asthma, tuberculosis, sensility, sex lassitude, impotence, epilepsy, dementia praecox, paranoia, diabetes, and locomotor ataxia. Forty-one persons had poor vision, and 32 of these saw things better after they had received a little goat testicle under the skin. This may be a valuable hint to the ophthalmologists. If there is any field of disease in which quantitative measurements of defects, and of improvements in defects can be made, it is in the field of vision. Do we find in this report that such quantitative measurements were made before and after the testicular injections? Not at all! The evidence for the goat testes making for keener vision in man runs like this:

"Thirty persons reported that their vision was greatly strengthened after the injection. One man declared that before his treatment he had difficulty in distinguishing the torpedo boats plying up and down the bay. Following two injections, he affirms he not only saw the torpedo boats, but that he could read the numbers on the bow. He is an accountant and credence should be given his statement."

Case 2.—At the recent International Physiological Congress in Edinburgh a European member of the Congress reported on rejuvenation of old billy goats, rams and men by testis transplants. The substance of the report was distributed as a printed pamphlet (French and English) to members of the congress. The pamphlet contained among other things photographic illustrations of these rejuvenations. The second and third figures depict an old ram before and after the testis graft. The photograph before grafting was taken shortly after the ram had been sheared. That after grafting was taken in a full coat of wool, and immediately after the ram had smelled of a yew (this is shown by the facial pose). Now, we know that even a young ram looks "woe-be-gone" for a time after shearing, and that a full coat of wool may

cover up signs of senility. Even castrated rams will investigate the yews by smelling and puckering the upper lip. An investigator presenting such pictures is either a simpleton, or else he is "manufacturing" evidence. In the research report in question two pages were glued together, as I thought by accident. But on looking over 50 or more copies of the pamphlet I found that the corresponding pages (20, 21) had been securely glued together in all of them. This intrigued me a great deal, for in some cases the pages could be separated enough to reveal that they contained photographs of a man. I was fortunate in securing one copy of the pamphlet in which the pasting had been done only in the corners so that the pages could be separated without destroying the photographs. These photographs (Figs. 7 and 8) showed a man at the age of 74 and 76, the latter being 18 months after receiving a testis graft. The photograph before grafting is not retouched, the man is unshaved, hair uncombed, mustache not trimmed, chin on chest, and there is no flower in his coat lapel. The photograph after grafting is retouched so that the features are as smooth as a billiard ball, the face is shaved, the mustache trimmed, the hair plastered down on the scalp, and head thrown back. The flower on his lapel further proclaims this septuagenarian the equal of any gay young blade on the Avenue d'Opera. Why did the author, evidently on second thought, wish to hide this striking proof of his thesis from members of the Congress? Did he possibly realize that it was too "raw" to be put over on a group of essentially scientific men?

These two cases referred to in some detail are typical of work done in ignorance, and, if not, in downright commercial dishonesty, at least in a "will to believe." Such work is a serious obstacle to progress in an inherently difficult field.

THE NEEDS IN CHICAGO IN NERVOUS AND MENTAL DISEASES

REPORT BY COMMITTEE OF INSTITUTE OF MEDICINE

There have been no outstanding historical features in the development of the study and treatment of nervous and mental diseases in Illinois. The main line of development may be readily visualized from the description of the present conditions. In common with other states dealing with humane treatment of the mentally handicapped, there has been a reorganization of state institutions, at first by the Board of Administration and later by the Department of Public Welfare. Certain custodial and reformatory institutions have been developed. There has been a betterment in juvenile court procedure. A psychopathic laboratory in connection with the Municipal Court has been created. Increased social service work has developed. A child study department has been included in the Department of Education. A State Psychopathic Hospital exists, and the Illinois Society for Mental Hygiene has attained an adequate organization. Psychiatry is a compulsory branch of the curriculum of our medical schools.

THE PRESENT SITUATION

There are approximately 18,500 insane persons in the State Hospitals for the Insane. There are about 5,000 feebleminded, epileptic and incorrigible persons in the state institutions. This makes a total of about 23,500 institutional cases.

In a survey of Nassau County, New York, 1,592 mentally abnormal persons were found, constituting 1.37% of the total population. Of these 946, or 0.82% of the entire population, were judged to require institutional care. Computing the cases in Illinois on this basis, 52,977 cases require institutional care. Obviously our institutional facilities are inadequate.

There are eight institutions for the insane in Illinois. Deducting the superintendents, whose work is largely administrative, and assistant superintendents, who are in effect sort of medical directors, we have about fifty physicians to care for 18,500 patients. Obviously there is a shortage of physicians.

There are 1,640 nurses and attendants, or about 1 to 11.3 patients. Only 50 have had competent psychiatric and general training. There is a state school of psychiatric nursing offering three courses to women

with proper qualifications—one a standard hospital course of three years, a short course of four months for senior students at general hospitals and a post-graduate course of six months for general hospital graduates.

The State Psychopathic Institute has a director and a staff consisting of an extramural pathologist with a technician, a serologist and a chemist. Recently the research work has been held somewhat in abeyance awaiting the completion of the new hospital buildings of the medical department of the University of Illinois.

The hospital at Dixon, created for the care of epileptic persons, has been given over to the feebleminded because of inadequate accommodations at Lincoln. A new institution is in course of construction.

In Cook County, we have the Psychopathic Hospital which constitutes the receiving service for the insane of this county. A rather important step forward has been taken in obtaining regular Cook County Hospital interns to serve a three months' internship in this ward. The nursing service has recently been placed under the charge of the Illinois Training School for Nurses.

There are three custodial institutions in Cook County—the County Jail, the Juvenile Detention Home and the House of Correction, all receiving inmates either pending some other disposition or for comparatively short terms. Considerable progress has been made in the Juvenile Court procedure. The Institute for Juvenile Research has filled a great need in connection with the problems of dealing with behavioristic difficulties of children. The staff of the institute contribute to the examination of children of the Juvenile Detention Home. Other cases are sent by courts, hospitals, practitioners, schools, social agencies and some are voluntary. The social service investigates and gives social treatment to cases from the State Training School for Girls at Geneva, the St. Charles School for Boys, the State School for the Feebleminded, the Kankakee State Hospital, the Chester State Hospital and Joliet Penitentiary. It is concerned with a number of problems of investigative nature, and some attention is given to teaching.

The group of reformatory institutions consists of the St. Charles and Geneva State Reformatories for Juvenile Delinquents and the House of the Good Shepherd.

What the Juvenile Court does for the county in the cases of juvenile offenders—boys under the age of 17 and girls under the age of 18—the Municipal Court in its various branches does for juniors above that

age. In connection with this court is a psychopathic laboratory which, because of some personal factors, holds an isolated position from other similar organizations.

Under the Department of Education there is a department of child study whose scope of work as outlined by the board is very broad. There are 120 rooms, each containing nineteen mentally deficient pupils, and forty rooms devoted to behavioristic cases. Children with an intelligence quotient below 50 are not received. These constitute about 10% of those applying. Of course, markedly deficient children are not brought to the school. Children are taught from an industrial aspect as well as from an educational aspect. The general aim is to put exceptional children back into the grades. The children are selected by the teachers in the grade schools, who, after observing them for 40 weeks, may report them as exceptional. The mental examinations are conducted by the Child Study Department, the examiners being 7 psychologists. They note in a general way the condition of the eyes, ears, teeth, etc. Physical examinations are made, as on normal children, by the Department of Health, and nursing service is rendered by the Department of Health school nurses, none of whom is a trained psychiatric nurse. No neurologic examination is made, and a comprehensive medical examination is not feasible. No psychiatrists are attached to the department. It is said that about one fourth of the cases so taught are turned back into the grade schools.

There is no provision for the registration of feebleminded in the State of Illinois.

Some small private noninstitutional agencies, as the Orthogenic Clinic of Rush Medical College, exist. In some cases the work is excellent, but the material is too limited to perform materially important service in relation to the need of the community.

The Illinois Society for Mental Hygiene serves the public in educational and propaganda work in mental health.

Social service is rendered by all institutions of the state. Outpatient clinics are held in Chicago, and similar facilities are afforded some of the other districts of Illinois. These clinics are held in Chicago once a week and in Jacksonville every two weeks. There is a social service department of Cook County which serves the Psychopathic Hospital and patients released or paroled from the Lincoln State School, the courts, the county jail, etc. Social service work is conducted in relation

to neurologic clinics in Chicago, but psychiatric social service work is inadequate. So-called social service work in most clinics and dispensaries consists largely of clerical work. For the most part, the social workers in these clinics and dispensaries have no special training in psychiatry.

There are practically no facilities in Chicago for training psychiatric social workers.

Despite the fact that many forms of insanity are distinctly medical problems and amenable to treatment, there are no psychiatric wards in any of our general hospitals.

In the City of Chicago may be found some so-called "rest cures" for the treatment of mental disorders. In most instances these rest cures consist of an old, abandoned residence containing a number of beds. Although these institutions receive a license from the Department of Public Welfare, there are no requirements as to the personnel, no medical staff need be resident, and the only requirement insisted on is the facility for affording comfortable and kindly attention. There are in the state a number of private sanitaria which are licensed by the Department of Public Welfare and from which quarterly reports are received. The only requirement in effect for license is that they treat their patients humanely, and it is expected that they will conduct an ethical practice.

In none of these institutions is there a minimum requirement of equipment, nursing staff, nurses training or medical staff. None of these institutions is graded as are the general hospitals in the country.

When a physician calls for the services of a nurse to assist in the care of a patient deficient mentally, it is found that many nurses sign against such cases, and such nurses as may not be called on as frequently as desired to care for general cases accept such services. There is no registration of psychiatric nurses or careful notation of special training.

Within the last few years the importance of teaching psychiatry has been recognized in our medical schools. Frequently, however, a good deal of this teaching is left to chance. Some of the schools have a minimum requirement for training in psychiatry. Clinical facilities for the teaching of psychiatry, particularly as related to mental deficiency and behavioristic defects, are wanting. There remains a considerable lack of coordination in the teaching of nervous and mental diseases. There are no scholarships or fellowships which have been offered in

neurology. Opportunity for research in the schools of medicine in the field of nervous and mental disease is conspicuous only by its absence.

INSTITUTIONAL CARE OF INSANE, FEEBLEMINDED AND EPILEPTIC

The Committee points out the need for additional institutional facilities in the care of the feebleminded and insane and the need for the establishment of the new institution for epileptic persons as one affording ample opportunity for research and adequate hospital treatment by competent physicians and with facilities for occupational training and direction.

The need for increasing the number and quality of physicians is pointed out. It must be urged that these physicians, from the superintendent down, should not be influenced by politics, that there be an assurance of tenure of position, chances for material promotion, adequate salaries, and suitable quarters for residence. There is need for a change of policy governing these institutions. Some plan should be evolved whereby real medical directors be placed in charge of the medical work of each institution unhampered by administrative details. The administrative department should be in close sympathy with the medical end, which should be the paramount consideration. Suitable laboratories should be constructed and full-time pathologists employed. Some of the physicians should have special training in medicine and surgery. Hospital wards should not be mere infirmaries. Graduate education in other hospitals and in universities should be encouraged and provided for. If the standard of medical work be increased, a plan of short course internships for general hospital interns may become possible. Closer contact with medical centers is urged.

It is recommended that senior nurse students of general hospitals be urged to avail themselves of the opportunity of the short course offered by the State School of Psychiatric Nursing. It is suggested that the standard of education (general) of nurses in state institutions be raised; and that special training in psychiatric nursing be increased. To accomplish this it will be necessary to make the service more attractive.

In relation to the appointment of medical directors of state institutions, it may be well to consider the feasibility of a plan whereby a committee representing the different medical schools of Chicago or Illinois may, in conjunction with the Civil Service Commission, have an appointive power.

PSYCHIATRIC WARDS IN GENERAL HOSPITALS

Establishment of psychiatric wards in general hospitals is urged and, if possible, wards for psychotic and maladjusted persons. We believe that such wards are needed, not only for the benefit of the patient, but in the interests of medical education. At the present time there are no facilities available for those mentally ill such as are afforded by a general hospital for the physically ill. On the one hand, we have the state institutions, and on the other, private sanitariums. The latter are conducted for profit. Few general hospitals which are well administered are self-supporting. There is need for endowed hospitals for insane and nonadjusted persons who are not proper patients for the psychiatric wards of a general hospital and who are capable of paying their way. Such an institution could give adequate medical, surgical and nursing service.

STANDARDIZATION OF REST CURES

It is recommended that so-called rest cures and private sanitariums for the treatment of nervous and mental diseases be standardized and, perhaps, rated as are general hospitals, for example, by the American College of Surgeons. These institutions should be inspected and graded as regards equipment, resident medical staff, attending staff, records, nursing staff, nurses training and laboratory work.

REGISTRATION OF PSYCHIATRIC NURSES

It is suggested that some arrangement be made whereby there will be registration of male and female nurses competent to take care of patients with mental disorder. We believe that nurses desiring to do such work and receiving such training as to be qualified for it should be passed on by some committee who could, in this way, give them a certain standing. Although this branch of nursing requires highly specialized training and more than average intelligence frequently, because of existing conditions, incompetent nurses are assigned to the care of mental cases.

CHILD WELFARE: MENTAL DEFICIENCY, PSYCHOPATHIC, CRIPPLED AND PARALYZED CHILDREN, ETC.

(a) The necessity for an extensive survey into the present inadequate and inconsiderate methods of teaching the mentally defective child is stressed. It is suggested that the Legislature be urged to

appropriate for such a survey to be made, perhaps, under the direction of the Institute for Juvenile Research or the Illinois Educational Commission in cooperation with the University of Illinois Department of Education, or the Department of Public Welfare. It is further recommended that the Department of Registration be informed of the necessity of such a survey relating not only to mental deficiency, but also to insanity, and that such a survey would be the logical first step in the investigation of the causes and treatment of insanity. This department has, at the present time, an appropriation for the study of insanity.

Based on such a study, recommendations may logically be made for a program including, perhaps, mental examination of backward school children, the mental clinic, the special class, instruction of parents of defective children, after-care of special class pupils, special training of teachers in normal schools, census and registration of the feebleminded, extra-institutional supervision for all uncaredfor defectives in the community, selection of the defectives who need segregation for institutional care, increased institutional facilities, parole for suitable institutionally trained adult inmates, mental examinations of persons accused of crime and of all inmates of penal institutions and long continued segregation of defective delinquents in special institutions.

It may be pointed out now that there is need for psychiatrists, physicians, trained psychiatric nurses and specially trained teachers and psychometrists in the Department of Education dealing with the teaching of mental defectives.

(b) *Clinics.*—It is suggested that as in the case of the insane, so with the feebleminded, psychopathic children, etc., it is necessary to create adequate outpatient departments in conjunction with dispensaries and hospitals and medical schools. Available for such clinics should be trained psychiatrists, neurologists, psychiatric nurses, social service workers and psychometrists. In this connection it is pointed out that better coordination with other clinical departments is necessary. Such a clinic may be the basis for a future development of an institution for defective children with proper facilities for thorough investigation, physical and mental, and for the direction of treatment.

(c) *Clinics for Crippled and Paralyzed Children.*—Similar facilities should be afforded crippled and paralyzed children. The Spaulding School for Handicapped Children fills, in a limited way, the need for such facilities on a large scale.

REHABILITATION

The insane, feebleminded and delinquent are placed, by statute, in the care of the state, but Cook County is vitally concerned in the efficiency of this care, both for the welfare of its citizens and economy in administration. It is not economy to provide mere housing for those who are handicapped. Many mental disorders can be cured; some conditions can be materially improved and the patient rendered capable of more or less complete self maintenance; others become progressively worse or cause permanent and complete disability. There is therefore need for variety in treatment. The general plan should be: (1) diagnosis and treatment of the disease or defect; (2) when treatment has accomplished all that is possible, training to fit the person to resume the fullest responsibility permitted by such handicaps as remain; (3) rehabilitation in industry, either in the community or in a specialized environment.

State and private institutions must be required to provide the treatment designated under (1) and (2) for such patients as are committed to their care. For persons with lesser degrees of mental disorder that do not require commitment, including the large class of persons with psychoneuroses, provision must be made in the clinics. At present, while diagnoses and medical or surgical treatment can be given, there is no provision for training, a lack that is keenly felt by all existing clinics. Facilities are needed for: occupational therapy; physical therapy; vocational training and training in recreation, group activities and citizenship. To provide these, there should be established an institution, or institutions, nonresident, to which patients would be sent on prescription of the clinics, contact to be maintained through social workers. They could well represent a stage in the return of full citizenship of patients released from state hospitals as well as those who have been treated as outpatients in the clinics.

The third and final stage, rehabilitation, means placing the patient, who has received all benefit possible from treatment and training, in an industrial environment suited to his capacity. This may be the ordinary business life of the citizen; but there is a large group of handicapped persons who are incapable, because of lack of initiative or energy, of competing with others on equal terms and yet are capable of productive labor. There are many such now confined in idleness in the state hospitals. Others have palsies and bodily defects from nervous disease which render competition difficult.

We believe that thought should be given to the possibility of establishing industrial colonies of village type in which there are possibilities for graded responsibility and elimination of the competitive features of the ordinary business life. From actual experience we know, for instance, that many of the patients now confined in state hospitals are quite capable of efficient factory work under proper supervision and can earn a living wage out of which could come the cost of supervision. In small towns with suitable factories and industries it should be possible to care for many such handicapped workmen by providing supervised homes or clubs in which the patient could live and pay his way. The principal obstacles depend on the attitude of organized labor which naturally objects to unfair competition, and the competition is unfair if labor is to be taxed to maintain the handicapped person. But if the proceeds of his work go toward his maintenance, this objection is not valid for it means reduction of the taxes. Another objection lies in the problem of workmen's compensation for injury in industry. Special provisions would have to be made to meet this difficulty.

The suggestions in the last paragraph are offered as possible measures for the relief of the handicapped man and also to diminish the constantly increasing burden of state hospitals and institutions for the dependent. They have been successfully established in some of the older countries. But whatever be done in regard to them, there is no doubt of the importance of establishing, in connection with the training center, a bureau for the placement of persons handicapped by mental or nervous disability in suitable employment.

EDUCATION

It is recommended that the Illinois Society for Mental Hygiene create a bureau of lecturers who shall offer their services for the purpose of addressing various audiences. They shall be available to all medical societies, whether branch societies of the Chicago Medical Society or special societies. They shall likewise be available to parents' and teachers' associations and to other groups interested in social welfare. Such lecturers may at times address organizations consisting of attorneys and jurists.

Joint meetings with the Bar Associations are urged.

It may be feasible to encourage lay education through the lay press and through the recent publication of the American Medical Association, *"Hygeia."*

MEDICAL EDUCATION

We believe there is urgent need for the standardizing of the teaching of the treatment of nervous and mental diseases in the medical schools. The members of this Committee are unanimous in the conviction that much time is wasted, much needless information crammed into medical students, and that the whole course beginning with the first year can be greatly improved by coordinating with the entire curriculum on this subject. For example, every one of us believes that the early teaching on anatomy and physiology of the nervous system is poorly planned. We find that when the students come to take up the clinical aspect of the nervous system they know entirely too little of the practical anatomy and physiology of the central nervous system.

Not only in relation to nervous and mental diseases but as well in relation to medicine in general there is a necessity for a more comprehensive understanding of human reactions. It is advised that a course in medical psychology be offered early in the curriculum, perhaps in the first clinical year, probably in conjunction with internal medicine. This course should be directed to the teaching of the reactions of persons to conditions, whether exogenous or endogenous.

It is suggested that there be a reorganization of the method of teaching preclinical subjects dealing with nervous and mental diseases to the end that there be closer cooperation of academic departments with the clinical departments dealing with nervous and mental diseases; that such subjects be taught by men who have clinical insight and would be favorable for close cooperation with teachers of clinical subjects.

It is recommended that there be a minimum requirement of 160 hours devoted to the teaching of nervous and mental diseases.

It is recommended that adequate provision be made for laboratory and research departments in nervous and mental diseases with the establishment of fellowships, scholarships, and additional clinics with full-time psychiatric social workers, nurses and psychometrists. Psychiatric wards in general hospitals should be established to furnish clinical material. The material at Cook County Hospital could be rendered more valuable by the establishment of a resident physician in the neurologic department. It is recommended that the material in the Cook County Infirmary and in the Psychopathic Hospital at Oak Forest be utilized. To this end it is suggested that resident physicians at the Cook County Infirmary be increased in number and by a change

of policy and added inducements improved in quality. A consulting staff should be appointed preferably by a committee of physicians representing the various universities.

The teaching of neurology and psychiatry should be placed on such a plane as to make possible graduate teaching such as outlined by the Committee on Graduate Instruction in Neuropsychiatry of the American Medical Association.

A. The basic general training in the undergraduate medical school should be at least that of Class A school, giving laboratory courses in neuro-anatomy, neurophysiology, neuropathology and instruction in psychology, clinical neurology and psychiatry. The number of hours recommended by the American Medical Association (105) for clinical instruction in neuropsychiatry is not sufficient, especially when the students have not been well prepared in the preclinical branches, with the result that the general practitioner is ordinarily lamentably ignorant of nervous diseases and especially of functional and behavior disorders which are by far most frequent in general practice. It might well be emphasized that even more important than the time element is that of competent instruction.

B. Courses leading to the specialty, which might be elective in the undergraduate medical school, should include advanced work in all of the above—yet it must be borne in mind that, with the crowded state of our present curricula, the student cannot hope to become sufficiently familiar with any one and much less with all of even the preclinical subjects and a considerable part of the postgraduate period must be set aside for additional work in the fundamental subjects. It must also be remembered that most men select their special field in medicine during the course of their internship or after entering practice and to such men electives in the undergraduate period will have had no special value. Considering also how important it is that specialists in neuropsychiatry should have a good understanding of general diagnostic procedures, particularly as applied in internal medicine, it is easy to see how a student may come to his postgraduate work relatively overweighted in his preparation for neurology but lacking in sufficient general foundation.

C. The hospital internship is an essential part of the preparation for specializing in neuropsychiatry and should be either a rotating general service or a service in internal medicine. The broader the understanding of general medicine and of pathology, the better specialist will the man be.

D. 1. Review courses in anatomy, physiology, pathology and psychology are not sufficient. Undergraduate instruction in the preclinical subjects, even when supplemented by electives, does not constitute a sufficient basis for subsequent specialization and any attempt merely to review these courses may result unsatisfactorily. Only extensive independent investigation in these subjects, wholly different from the didactic work of the undergraduate period, will suffice.

A much closer correlation than is usually found is needed between the clinical and preclinical subjects and work in the latter field should be directed by one who is at least in sympathy with and able to appreciate the clinician's viewpoint. In other words in neuro-anatomy, neurophysiology and neuropathology, the instructor should have in mind intergration, localization and clinical application, and should teach them as applied science rather than as pure science. In even greater degree is it necessary to bring psychology, as

ordinarily taught, into close relationship with the needs of one who will ultimately engage in the practice of medicine. Research in human behavior as a field of psychology is just beginning and yet it is this which the medical student really needs. Considering the lack of clinicians qualified to teach the laboratory branches, the necessary correlation can probably be better secured by proper cooperation between the laboratory and clinical teachers than through the assumption of the preclinical branches by the latter.

2. With his five years' preliminary training, the graduate student ought to be largely beyond the need of didactic instruction, and his work should be that of an independent student, yet so arranged as to cover the following:

(*a*) Neuro-anatomy: Embryologic development of the nervous system; gross and microscopic anatomy of the brain, the cord and the vegetative nervous system; the origin, course and distribution of the cranial and spinal nerves.

(*b*) Neurophysiology: Physiology of the special senses, of common sensation, of nerve muscle preparations, of the spinal cord and brain and of the vegetative nervous system.

(*c*) Neuropathology: Finer histopathology of the nervous system, the coarser tract lesions, gross morbid anatomy of the brain and cord with special applications to particular diseases and the serology of the spinal fluid.

(*d*) Psychology: Abnormal psychology and practical experience in psychometric examinations.

(*e*) Physiological chemistry, legal medicine and sociology should be elective.

These courses, with possibly a limited amount of clinical work, should occupy the full time of the first academic year (eight months) and the ensuing fourteen months (making a total of two years and eleven months each) should be applied in equal parts to clinical work in neurology and in psychiatry, including also, work in neuro-ophthalmology and neuro-otology. These clinical courses should be designed not to attempt a finished training of the applicant in either branch of neuropsychiatry but to give basic instruction in both since the range of the two specialties so overlap in practice that this need must be met. Instruction in this period should be chiefly through bedside work and practical experience.

At the completion of two years (of eleven months each) the student's work, if satisfactory, should be recognized by the degree of master of science in neuropsychiatry, if this degree will be granted by the graduated school of the institution where the course is completed or otherwise, by a certificate outlining the work accomplished.

3. The two years' course is designed to give basic general training in the combined field of neuropsychiatry and the third year may be a continuation of this work, but if the student decides to perfect himself especially in either neurology or psychiatry, the third year of eleven months may be applied to the branch selected. If a thesis is to be included, and this is generally required in any school where the Ph.D. degree is given, it should be completed in the third year. The thesis will deal with either clinical or laboratory material and will constitute a major subject. A minor may be chosen from some allied subject. The satisfactory completion of the third year should lead to a degree of Ph.D. if the graduate school of the institution concerned will accept the work offered —otherwise, its completion should be recognized by a proper certificate.

4. In addition to the major and minor of the third year, the student should be attached to an institution in which high grade work in neurology or psychiatry or both is being carried out. Such an institution, in addition to an

adequate number of beds, will have a competent staff, a laboratory in which neurology and neuropathology are studied and taught and will also have an outpatient and a social service department. Internship or assistantship in such an institution is a *"sine qua non"* for the prospective specialist.

5. Most of the men who undertake these courses will ultimately be teachers and if, in the course of their training, they are placed as assistants in the department of anatomy, physiology and pathology during the periods that the nervous system is being studied, a better correlation is secured and the prospective neuropsychiatrist becomes better trained in these subjects, for teaching is the best method of learning. Yet teaching must not be allowed to monopolize the student's time and most of his work will consist in acquiring greater clinical experience and in studying special problems.

6. The idea of training men for original investigation should never be lost sight of but this investigation is not necessarily limited to laboratory fields. Men should be taught to weigh evidence, to determine the relative value of symptoms, the factors of observation and, in general, to distinguish between real science and pseudo-science.

7. Each individual teaching center should give complete courses and these courses should be coordinated as much as possible but some schools or centers offer better opportunities for certain lines of work than others and some men will offer courses which cannot be duplicated elsewhere. It would, therefore, be of decided advantage to the prospective neuropsychiatrist if he could obtain his instruction in more than one school and thus have contact with as many men as possible during his training. A central bureau of information should be established through which lists of vacancies and other data could be provided and through which a candidate for a career in neuropsychiatry would obtain the best possible chance to become properly trained.

8. The question of neurosurgery deserves special consideration. Those undertaking this field should be primarily neurologists, having had the neurological training as outlined above, plus a surgical internship or assistantship.

9. Shorter courses, of a year for example, with the time divided equally between preclinical and clinical subjects, may be useful if the intention is merely to supplement a deficiency in the undergraduate training. If the work is designed to fit the applicant to specialize in either neurology or psychiatry, with due allowance for the deficiency in the undergraduate work, three years is necessary.

10. A too rigidly prescribed course to be required of everyone entering the practice of neuropsychiatry must be avoided. Standards are essential but there will always be those of exceptional ability or whose peculiar experience may have been such as to amply qualify for practice, teaching and research even though they may not have had the benefit of a well planned and well balanced period of study and the time will always vary with the preliminary attainments and native ability of the student. Accomplishment rather than time spent should be the determining factor in deciding on fitness. Yet all this constitutes no reason why a well planned and well balanced course of study may not be available to those who desire to fit themselves for a course in neuropsychiatry.

E. Already answered.

F. Neither certificate nor degree should be awarded for short courses. When granted they are often misused and made to possess a significance very different from that originally intended.

G. Degrees, if granted at the completion of a full three years' course should be coordinate with those of other specialties and there might be separate degrees for neurology and for psychiatry or one for both. The regulations determining the granting of a graduate degree should be left to the school in which the graduate work is completed.

H. Qualification for the practice of a specialty should be left to the state and national boards of examiners, possibly advised by national societies representing those most highly qualified in the specialty.

MEDICOLEGAL

Recommendations dealing with this subject will probably be offered by the Committee on Medico-Legal practice. This Committee feels that a few suggestions may properly be advanced at this time.

It is thought desirable to have passed in the Legislature a bill providing for the appointment of a commission to investigate the laws of this state, the resolutions to approximate that ones here reproduced.

WHEREAS, One of the great responsibilities placed on the State of Illinois is the care, treatment, hospitalization and protection of insane and others in this state affected with like mental incapacity, a subject that notwithstanding the marked progress of psychiatry, has not been given adequate consideration in this state; and

WHEREAS, It is desirable to make necessary revision of the laws in this state on the subject, and also to make provision for properly discharging this great responsibility of the state, and attempting a solution of the difficulties arising from the problem of the insane in this state; therefore, be it

Resolved, By the House of Representatives of Illinois, the Senate concurring therein, that a Commission consisting of eleven (11) persons shall be appointed as follows:

Five (5) members thereof to be appointed by the Speaker of the House of Representatives (of which three (3) shall be psychiatrists of recognized ability in this state);

Five (5) members thereof to be appointed by the President of the Senate three (3) of whom shall be psychiatrists of recognized ability in this state); and

One (1) member of said commission shall be appointed by the Chairman of the Board of Administration of Illinois;

to make a careful examination and investigation of the subject of the care, treatment, hospitalization and protection of insane persons now or hereafter in this state, including the examination and investigation of the laws of this state, both civil and criminal relating to the defense of such persons, in criminal cases and to the personal and property rights of such persons.

The Commission so created and hereby authorized shall have full power to inquire into the subject fully and in detail and for the purpose of conducting such investigation such Commission is hereby authorized and empowered to subpoena witnesses under the signature of the Chairman and place under oath and examine such witness, and to issue subpoena *duces tecum* for witnesses

and for such books, documents, papers and memorandum or other things that such Commission shall deem necessary for its information in carrying out the objects and purposes of this resolution.

Said Commission shall report its conclusion, findings and recommendations to the General Assembly and shall recommend such proposed legislation or other action as may be deemed necessary arising out of the subject matter of the inquiry.

Such Commission is authorized to employ such assistants as it may require, including the employment of clerical, statistical, technical, legal and medical experts. The specific enumeration of the powers of this commission shall not in any way limit the authority of the Commission to investigate any and all matters entering into the subject hereof, and the purpose for which this Commission is created.

The members of said Commission shall serve without compensation for such services, but shall be entitled to the actual expenses incurred by them during the performance of the duties enjoined by this resolution.

Resolved Further, That the General Assembly proceed to make an appropriation in the sum of $..... for the necessary expenses for carrying out this resolution; that all vouchers for expenses of such Commission and its members shall be approved by the Chairman of the Commission, the Speaker of the House of Representatives and the President of the Senate.

It is recommended that adequate provision be made in the County Jail for the observation of all patients remanded to the jail and particularly for cases in which the plea of insanity is entered. This necessitates the construction of an observation ward and the employment of a full-time resident psychiatrist. This physician should never be called to testify in Court but may be called on by the Commission which is mentioned below. He should be appointed by the Cook County Commissioners through the Cook County Hospital Staff.

It is recommended that the criminal insane, when recommended for discharge or parole by the superintendent of the institution to which they have been committed, be examined by a commission before such parole or discharge be granted.

The Committee endorses, with such few revisions as are indicated by underlined matter appearing in parenthesis, the Criminal Responsibility Bill and Expert Testimony Bill drafted by a Committee of the American Institute of Criminal Law and Criminology, which are here appended.

In relation to the Expert Testimony Bill, the Commission appointed by the court should have power to serve subpoenas, power to administer oaths and power to demand the production of documents.

Relative to the written report, attention is called to the fact that any history which is obtained from persons other than the accused is hearsay and does not not constitute admissible testimony.

Relative to the Criminal Responsibility Bill, it is suggested that when mental disease is proposed as a defense the plea of insanity must be entered before the trial. On good cause shown the plea of insanity may be made during a trial and under that condition the trial may be continued to afford opportunity for the appointment of a commission to examine and report on the condition of the prisoner. This same provision should apply to cases wherein the person becomes insane while awaiting trial or punishment.

It is suggested that provision be made, if possible, for appeal from habeas corpus proceedings. Frequently a misinformed judge may release a potentially dangerous insane man. Provision could be made for change of venue to a probate judge.

CRIMINAL RESPONSIBILITY BILL

Sec. 1. *When Mental Disease Is a Defense.*—No person shall hereafter be convicted of any criminal charge when at the time of the act or omission alleged against him he was suffering from mental disease and by reason of such mental disease he did not have the particular state of mind that must accompany such act or omission in order to constitute the crime charged.

Sec. 2. *Form of Verdict.*—When in any indictment or information any act or omission is charged against any person as an offense, and it is given in evidence on the trial of such person for that offense that he was mentally diseased at the time when he did the act or made the omission charged, then if the jury before whom such a person is tried concludes that he did the act or made the omission charged, and by reason of his mental disease was not responsible according to the preceding section, then the jury shall return a special verdict that the accused did the act or made the omission charged against him but was not at the time legally responsible by reason of his mental disease.

Sec. 3. *Inquisition.*—When such special verdict is found, the court shall remand the prisoner to the custody of (the proper officer) and shall immediately order an inquisition by (the proper persons) to determine whether the prisoner is at that time suffering from a mental disease so as to be a menace to the public safety.

EXPERT TESTIMONY BILL

Sec. 1. *Summoning of the Witnesses by Court.*—Whenever in the trial of a criminal case the issue of insanity on the part of the defendant is raised, the judge of the trial court may call one or more disinterested qualified experts, not exceeding three, to testify at the trial (*and if the judge does so, he shall notify counsel of the witnesses so called, giving their names and addresses*). (Omit this.) On trial of the case, the witnesses called by the court may be examined regarding their qualifications and their testimony by counsel for the prosecution and defense. Such calling of witnesses by court shall not preclude the prosecution or defense from calling other expert witnesses at the trial. The witnesses called by the judge shall be allowed such fees as in the discretion of the judge

seem just and reasonable, having regard to the services performed by the witnesses. The fees so allowed shall be paid by the county where the indictment was found.

Sec. 2. *Written Report by Witnesses.*—When the issue of insanity has been raised in a criminal case, each expert witness, who has examined or observed the defendant, may prepare a written report regarding the mental condition of the defendant based on such examination or observation, and such report may be read by the witness at the trial after being duly sworn. The written report prepared by the witness shall be submitted by him to counsel for either party before being read to the jury, if request for this is made to the court by counsel. If the witness presenting the report was called by the prosecution or defense, he may be cross-examined regarding his report by counsel for the other party. If the witness was called by the court, he may be examined regarding his report by counsel for the prosecution and defense.

Sec. 3. *Commitment to Hospital for Observation.*—Whenever in the trial of a criminal case the existence of mental disease on the part of the accused, either at the time of the trial or at the time of the commission of the alleged wrongful act becomes an issue in the case, the judge of the court before whom the accused is to be tried or is being tried *(shall commit the accused to the State Hospital for the Insane, to be detained there for purposes of observation until further order of court. The court shall direct the superintendent of the hospital to permit all the expert witnesses summoned in the case to have free access to the accused for purposes of observation. The court may also direct the chief physician of the hospital to prepare a report regarding the mental condition of the accused. This report may be introduced in evidence at the trial under the oath of said chief physician, who may be crossed-examined regarding the report by counsel for both sides.)* (It would be well to so word this section as to exclude the above italicized parts and substitute provision for competent observation and examination in the county jail: First, because if the accused is committed to a State Hospital for the Insane he is automatically declared not guilty and may be subject to discharge by the superintendent of the institution; and, second, great difficulty may be experienced in taking the accused out of the custody of the sheriff.)

LEWIS J. POLLOCK, Chairman.
HUGH T. PATRICK.
THOR J. ROTHSTEIN.
H. DOUGLAS SINGER.
PETER BASSOE.
RALPH C. HAMILL.

FOURTH ANNUAL REPORT TO GOVERNORS OF THE INSTITUTE OF MEDICINE OF A COMMITTEE APPOINTED TO INQUIRE INTO THE QUESTION OF NECROPSIES IN THE HOSPITALS OF CHICAGO

The survey of necropsies in the hospitals of Chicago for 1922 shows a continued increase of interest of the hospital staffs in the work of the hospitals. Thirty-seven of the hospitals having a bed capacity of 50 or more responded to the 1922 questionnaire. The capacity of the reporting hospitals for 1922 was 7,543 beds. There were 174,590 admissions and 7,844 deaths. Permission necropsies were made in 1,422 cases as against 1,206 in 1921, 872 in 1920, and 789 in 1919. In addition to permission necropsies, coroner's necropsies were made in 1,011 cases, including 756 cases at Cook County Hospital; these have not only yielded medicolegal information, but also have been of great value in teaching and the improvement of clinical diagnosis and treatment.

In the computation of percentages of permission necropsies, the figure taken for number of deaths is the actual number of deaths (not including still births) minus the coroner's necropsies. This more accurate measure of permission necropsies is made possible by the obtaining of data of coroner's necropsies in 1922, more complete than in previous years. This change modified the figures for the several hospitals but slightly, and does not materially affect their relative values in any year.

The percentage of permission necropsies for 1922 for all reporting hospitals was 20.8. Omitting the figures for Cook County Hospital, there were 833 permission necropsies and 255 coroner's necropsies in the other hospitals in 4,430 deaths (19.9% permission) as against 663 in 1921, 556 in 1920 and 474 in 1919, an increase of 75% in 3 years.

While these figures show an encouraging increase in pathologic study in the reporting hospitals, the situation is much less favorable in the group of 10 hospitals which failed to respond. With one or two exceptions, interest in necropsies is at a low ebb, so that few necropsies are made. Assuming that the admissions and deaths bear the same relation to bed capacity as in the reporting hospitals, there were approximately 1,000 additional deaths, with a very small number of necropsies.

Hospital	Beds	Patients	Deaths	Necropsies		Percentage Permission				Pathologist
				Permission	Coroner	1922	1921	1920	1919	
Alexian Brothers	285	No report	No report	No report	No report	....	....	7.4	4.9	
American	140	4,113	118	9	4	7.9	8.1	2.9	12.1	H. Rosenberg
Augustana	260	4,081	200	23	...	12.5	9.0	4.5	3.7	J. W. Nuzum
Durand	60	894	44	21	0	47.7	44.0	37.1	24.4	L. Hektoen
Chicago Fresh Air	104	No report	No report	No report	No report	....	2.2	6.8	....	
Chicago Lying-In	260	6,172	59	36	1	62.1	36.3	41.3	8.0	W B. Serbin
Chicago Memorial	149	2,878	77	19	4	26.0	28.4	....	....	O. T. Schultz
Children's Memorial	185	2,637	214	50	4	23.8	37.5	35.4	23.1	W. B. Hibbs
Columbus	150	3,294	64	13	2	20.9	7.6	5.7	....	C. O. Getty
Columbus Extension	75	No report	No report	No report	No report	....	....	6.9	....	
Contagious Disease (Municipal)	450	3,918	184	1	0	0.5	3.9	6.8	....	
Cook County	2,500	42,968	3,414	589	756	22.1	26.8	12.7	8.9	W. B. Moody
Englewood	150	4,089	163	10	8	6.4	....	....	....	L. F. DeSaunier
Frances Willard	120	3,208	111	2	...	1.8	2.3	2.4	0.0	S. M. Feinberg
Garfield Park	102	2,896	68	0	2	0.0	0.0	0.0	0.0	R. L. French
German Evangelical Deaconess	54	2,082	102	2	3	2.0	....	0.0	2.0	W. H. Buhlig
Grant	150	No report	No report	No report	No report	....	....	....	....	
Henrotin Memorial	75	No report	No report	No report	No report	....	2.6	....	....	
Home for Destitute Crippled Children	110	1,140	2	0	0	0.0	0.0	0.0	0.0	
House of Correction	75	1,445	35	12	23	100.0	....	....	....	E. R. LeCount
Illinois Central	100	2,817	80	13	23	22.8	16.6	9.7	3.2	A. H. Baugher
Isolation (smallpox)	35	102	13	0	0	0.0	0.0	....	....	
Lakeside	85	No report	No report	No report	No report	....	....	11.4	0.0	
Lutheran Deaconess	100	2,298	80	9	1	11.4	....	....	....	I. Pilot
Mercy	400	6,809	205	23	20	12.4	28.5	13.0	....	Dr. Arnold
Michael Reese	461	9,348	358	125	20	36.9	16.1	10.9	9.0	O. T .Schultz
North Chicago	84	2,183	68	19	3	29.2	18.3	5.8	?	B. H. Orndoff
Norwegian Deaconess	150	4,656	140	35	11	27.1	7.0	2.7	0.0	W. G. Hibbs
Passavant	75	2,635	98	5	13	5.9	0.0	5.3	0.0	D. H. Ecke
Peoples	40	1,122	45	0	...	0.0	0.0	0.0	0.0	E. C. Riebel
Post Graduate	88	1,691	63	5	3	8.3	....	....	....	E G. Kirk
Presbyterian	437	10,098	276	194	5	71.6	49.2	52.2	48.4	H. A. Oberhelman
Provident	65	No report	No report	No report	No report	....	5.1	....	....	
Ravenswood	41	1,500	44	2	13	6.4	5.5	19.6	13.6	J. J. Moore
Robert Burns	40	No report	No report	0	1	0.0	....	....	....	None
St. Anne's	100	3,003	153	10	6	6.8	5.2	3.0	2.1	E. Weiss
St. Anthony de Padua	189	5,174	166	2	5	1.2	2.5	1.2	4.7	F. B. Olentine
St. Bernard's	200	No report	No report	No report	No report	....	....	....	....	
St. Elizabeth's	225	4,213	220	10	28	5.2	7.1	1.6	....	F. L. Pickof
St. Joseph's	175	4,454	144	43	1	30.0	17.3	18.1	21.4	L. E. Hines
St. Luke's	410	9,836	263	92	10	36.3	29.4	20.1	17.6	E. F. Hirsch, E. R. LeCount
St. Mary of Nazareth	200	4,829	211	6	28	3.3	0.8	0.7	....	F. B. Lusk
U. S. Marine No. 5	125	785	23	3	0	13.0	50.0	16.6	21.4	
University Hospital (Lincoln St.)	100	2,142	53	0	1	0.0	0.0	3.4	....	
Washington Park	110	No report	No report	No report	No report	....	....	....	3.2	
Washington Boulevard	85	No report	No report	No report	No report	....	5.1	7.0	8.2	
Wesley	275	6,517	221	49	11	23.3	23.5	15.3	7.9	C. A. Barnes
West Side	155	No report	No report	No report	No report	....	0.0	0.0	0.0	
Womens and Childrens (Mary Thompson)	93	2,042	35	0	1	0.0	9.1	31.2	7.1	Norma Piper

The estimated percentage of permission necropsies for all the 47 hospitals is thus 18%, a number far below that possible when even moderate attention is given to this important source of medical instruction.

In 1922, fifteen hospitals showed an increase in percentage of necropsies over 1921. In 14 hospitals the percentage of permission necropsies was over 20 (71.6, 62.1, 47.7, 36.9, 36.3, 30.0, 29.2, 27.1, 26.0, 23.8, 23.3, 22.8, 22.1, 20.9) as against 9 hospitals having over 20% in 1921, and 6 in 1920. In addition, at the House of Correction hospital, necropsy is held in all cases.

The result of sustained effort to improve the work of hospitals is seen in the progressive increase in permission necropsies from year to year. The patients received in these hospitals do not differ in race, religion or degree of intelligence from patients entering other hospitals in which necropsies are rarely held. The chief difference between the two groups of hospitals lies in the difference in attitude of staffs. In some instances in both groups of hospitals, undertakers either through ignorance or deliberate design attempt to hinder the work of the hospitals in obtaining of necropsies. This obstacle can be overcome to a large extent by seeing to it that the activities in the hospital of such ignorant undertakers are restricted until their unjustified attitude is modified.

Through movements to standardize hospitals there has come a general improvement in laboratory facilities, with resulting improvement in routine clinical laboratory work and the examination of tissues. In some hospitals in which the equipment meets the required standards on paper, this equipment is not utilized, and it is assumed that the laboratory will run itself without the sustained interest of the staff. It is frequently in these hospitals that necropsies are also neglected, and the actual efficiency of the staff in the care of patients too often reflects the indifference of the staff to methods of improving their own professional ability. The percentage of necropsies is thus frequently an index of the standard of work in the hospital.

Twelve hospitals report that now a weekly pathologic conference attended by members of the staff is held. Eight others report monthly pathologic conferences The examination of fresh material at weekly conferences, at which the relation of clinical findings with those at necropsy is studied and discussed, is of enormous value to hospital progress. In this study, the importance of a complete necropsy report is evident. In this connection figures were obtained for 1922, showing

that of 1,287 permission necropsies, 514 were complete and included examination of the head. In the remainder, the necropsy was complete with the exception of the head, or in a few instances, the thorax, abdomen or head only was examined. It is recognized that sometimes the permission for necropsy is restricted, and here a partial necropsy is better than none, but in general the importance of complete examination is obvious.

The Committee desires again to thank superintendents and staffs of the hospitals for their cooperation in a survey which it is believed will continue to be of help in the progress of medicine.

D. J. DAVIS
J. P. SIMONDS
A. B. KANAVEL
A. FRICK
E. E. IRONS, Chairman.

ANNOUNCEMENTS

Extract from the minutes of the meeting of the Board of Governors, held Dec. 10, 1923:

"Dr. Frank Billings presented to the Institute of Medicine $10,000 as an endowment in perpetuity under the following provisions: $5,000 to be maintained by the Institute as the Lewis Linn McArthur Fund; $5,000 to be maintained by the Institute as the Ludvig Hektoen Fund; the annual income from each of the two funds to be expended in the promotion of clinical investigation in internal medicine or in payment of honorariums for lectures delivered before the Institute or for other purposes as the Board of Governors may deem expedient and wise. In the event that the Institute of Medicine should cease to exist the terms of the gift provide that the endowment be turned over to a university maintaining a medical school incorporated in the State of Illinois provided the university accepting the gift or trust agrees to carry out the provisions mentioned in the foregoing."

The terms of the above gift are set forth in an agreement signed by the donor, Dr. Billings, by the Chairman and the Secretary of the Board, and deposited by the Treasurer with the securities of the Institute.

Dr. Pusey moved that the Board accept for the Institute this generous gift and that a formal letter of thanks be sent to Dr. Billings, and that he be made a Benefactor of the Institute as provided in the constitution and by-laws. This motion was seconded by Dr. Herrick and carried.

At the annual meeting of the Institute, Dec. 4, 1923, Julius H. Hess, Arthur D. Black, and J. P. Simonds were elected governors to serve for five years.

At the annual meeting of the Board of Governors, Dec. 10, 1923, officers for 1924 were elected as follows: President, Cassius D. Wescott; Vice-President, Isaac A. Abt; Chairman of the Board, L. Hektoen; Secretary, George H. Coleman; Treasurer, Joseph A. Capps; Membership Committee, Theodore Tieken, D. J. Davis, J. Gordon Wilson, J. P. Simonds, and J. A. Capps.

The next Pasteur Lecture will be given by Prof. William H. Howell of Johns Hopkins University.

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GERSTS